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

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ABSTRACT

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

OBJECTIVES This study sought to investigate the comparative effectiveness of abbreviated (1 month) vs standard (≥3 months) APT in HBR patients with and without DM after biodegradable polymer sirolimus-eluting coronary stent implantation.

METHODS This was a prespecified analysis from the MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With a Abbreviated Versus Prolonged DAPT Regimen) trial, which randomized 4,579 HBR patients (1,538 [34%] with DM) to abbreviated (n = 2,295) or standard (n = 2,284) APT. The coprimary outcomes were net adverse clinical events (NACEs; composite of all-cause death, myocardial infarction, stroke, and major bleeding), major adverse cardiac or cerebral events (MACCEs; all-cause death, myocardial infarction, and stroke), and major or clinically relevant nonmajor bleeding at 11 months.

RESULTS HBR patients with DM had higher risks of MACCEs (HR: 1.28; 95% CI: 1.00-1.63) and similar net adverse or bleeding events compared with nondiabetic subjects. Abbreviated compared with standard APT was associated with similar NACEs and MACCEs ($P_{interaction}$ = 0.47 and 0.59, respectively) and reduced major or clinically relevant nonmajor bleeding ($P_{interaction}$ = 0.55) irrespective of diabetes status.

CONCLUSIONS MACCE and NACE rates were similar, and bleeding rates were lower with abbreviated APT in patients with or without diabetes. Therefore, diabetes status did not modify the treatment effects of abbreviated vs standard APT in HBR patients after biodegradable polymer sirolimus-eluting coronary stent implantation. (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With a Abbreviated Versus Prolonged DAPT Regimen [MASTER DAPT]; NCT03023020) (JACC Cardiovasc Interv. 2024;17:2664-2677) © 2024 by the American College of Cardiology Foundation.

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Diabetes mellitus (DM) is a condition of global importance with its prevalence 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 pharmacologic, interventional, and surgical treatments,[3,4] DM remains an independent predictor of ischemic complications after 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, a higher prevalence of multivessel involvement with diffuse and long lesions, left main and bifurcation 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 the current guidelines, the choice and duration of antithrombotic treatment after 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 dual antiplatelet therapy (DAPT) duration after PCI for the prevention of ischemic and bleeding complications in high bleeding risk (HBR) patients remains unsettled.

The MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen) trial randomized HBR patients who underwent the implantation of a biodegradable polymer sirolimus-eluting stent to abbreviated (1 month) or standard (≥3 months) antiplatelet therapy (APT).[12] In the overall patient population, abbreviated APT was noninferior to treatment continuation for at least 2 additional months for the occurrence of net adverse clinical events (NACEs) and major adverse cardiac and cerebral events (MACCEs) and reduced major or clinically relevant nonmajor bleeding (MCB).[12-15] These findings were corroborated by multiple meta-analyses.[16,17] In this prespecified analysis from the MASTER DAPT trial, we sought to investigate whether the treatment effects of abbreviated vs standard APT in unselected HBR patients would be affected by the presence of DM.

ABBREVIATIONS AND ACRONYMS

APT = antiplatelet therapy
CAD = coronary artery disease
CVA = cerebrovascular accident
DAPT = dual antiplatelet therapy
DB = diabetes mellitus
MACE = major adverse clinical event(s)
MACCE = major adverse cardiac and cerebral event(s)
MCB = major or clinically relevant nonmajor bleeding
MI = myocardial infarction
NACE = net adverse clinical event(s)
OAC = oral anticoagulation
PCI = percutaneous coronary intervention
SAPT = single antiplatelet therapy
ST = stent thrombosis

METHODS

STUDY DESIGN. This is a prespecified analysis of the MASTER DAPT (NCT03023020) trial, an investigator-initiated, randomized, open-label, noninferiority trial with sequential superiority testing enrolling an unselected patient population at HBR after the implantation of a biodegradable polymer-coated Ultimaster (Terumo Corporation) sirolimus-eluting stent.[12,18] The trial was approved by the Institutional Review Board at each participating site, and all

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patients provided 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 Methods.

STUDY POPULATION. Patients at HBR who underwent treatment of all coronary lesions requiring revascularization with an 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 DAPT) during the first month after the index PCI were eligible for trial participation. HBR criteria are shown in the Supplemental Methods.[19]

The key exclusion criteria were the implantation of a stent other than an 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 Methods. Patients were considered diabetic if they were on a diet or undergoing 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 and 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 months of oral anticoagulation (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 6 months after the index procedure. Patients allocated to the standard treatment group continued DAPT for at least 5 additional months (ie, 6 months after the index procedure) or, for those receiving OAC, for at least 2 additional months (ie, 3 months after the index procedure) followed by SAPT.

OUTCOMES. The 3 ranked coprimary outcomes were 11-month NACEs (a composite of death from any cause, MI, stroke, or major bleeding), MACCEs (a composite of death from any cause, MI, or stroke), and MCB (a composite of Bleeding Academic Research Consortium type 2, 3, or 5 bleeding). The secondary outcomes included the individual components of the 3 coprimary outcomes, death from cardiovascular or noncardiovascular causes, transient ischemic attack, definite or probable stent thrombosis, and all bleeding events. All events were adjudicated by an independent adjudication committee that was unaware of the treatment allocations. All data were stored in a central database (Department of Clinical Research, University of Bern).

STATISTICAL ANALYSIS. The data were analyzed according to the intention-to-treat principle. Outcomes were assessed separately for patients with or without diabetes by calculating HRs with 95% CIs. For patients with a primary outcome, the 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, the time to censoring was defined as the difference between the dates of the last known clinical status and randomization plus 1. The Com-Nougue method was used to analyze the time to the event with day 0 defined as the date of randomization at the 1-month visit and up to 335 days later. 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. HRs and 95% CIs were generated for the primary and secondary outcomes with the use of Cox proportional hazards regression analysis with censoring at the end of the study and at the time of death. The proportional hazards assumption for the Cox proportional hazards model was evaluated using Schoenfeld residuals.[20] Associations of DM with bleeding and/or ischemic outcomes were also adjusted for clinically relevant differences among patients with and without diabetes. *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 1 df. An additional prespecified subgroup of interest was the need for OAC. The 95% CIs and *P* values for interaction were not adjusted for multiplicity and should not be used to infer definitive treatment effects. The analyses were performed using Stata 16.0 (StataCorp LLC).

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 DM and 3,041 (66%) without DM were randomized at a median of 34 days post-PCI (Q1-Q3: 32-39 days) to abbreviated (n = 2,295 patients [diabetics: n = 754 and nondiabetics: n = 1,541]) or standard (n = 2,284 [diabetics: n = 784 and nondiabetics, n = 1,500]) APT (Supplemental Figure 1). DAPT composition and the type of SAPT did not differ among patients with and without DM (Supplemental Tables 1 and 2). Detailed information on antiplatelet use in diabetic and nondiabetic patients is shown in Supplemental Figures 2 and 3.

BASELINE AND PROCEDURAL CHARACTERISTICS. Compared with nondiabetic individuals, patients with DM were younger; had higher body mass index; and had more cardiovascular risk factors such as prior atherosclerotic disease, including prior stroke and peripheral arterial, carotid, and coronary disease (ie, 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 (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) 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 transradial access and direct stenting but more frequent intravascular ultrasound use and lesion postdilatation in DM patients (Supplemental Table 4). Baseline and procedural characteristics according to DM and the randomized treatment regimen were well-balanced between the groups, except for a higher prevalence of male patients 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 (243/754 [32.2%]) than standard (199/784 [25.4%]) APT ($P = 0.003$).

CLINICAL OUTCOMES BY DIABETES. At the 11-month follow-up (**Table 1**), NACEs occurred in 130 of 1,538 diabetic patients (8.50%) and in 224 of 3,041 nondiabetic patients (7.39%) (HR: 1.15; 95% CI: 0.93-1.43; $P = 0.19$; adjusted HR: 1.14; 95% CI: 0.79-1.64; adjusted $P = 0.48$). The rate of MACCEs was higher in diabetic compared with nondiabetic patients (108/1,538 diabetic [7.06%] vs 168/3,041 nondiabetic [5.55%] patients; HR: 1.28; 95% CI: 1.00-1.63; $P = 0.05$; adjusted HR: 1.22; 95% CI: 0.79-1.87; adjusted $P = 0.37$), whereas MCB occurred in 125 of 1,538 diabetic patients (8.25%) and in 234 of 3,041 nondiabetic patients (7.79%) (HR: 1.06; 95% CI: 1.06-1.32; $P = 0.60$; adjusted HR: 1.16; 95% CI: 0.83-1.61; adjusted $P = 0.39$). 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 coprimary or other secondary outcomes.

CLINICAL OUTCOMES BY DIABETES AND RANDOMLY ALLOCATED ANTIPLATELET REGIMENS. Clinical outcomes at 11 months in diabetic and nondiabetic patients stratified by APT are shown in **Figures 1 and 2**. NACEs did not differ in the abbreviated and standard APT groups among diabetic patients (65/754 [8.67%] vs 65/784 patients [8.33%]; HR: 1.04; 95% CI: 0.74-1.46; $P = 0.83$) and nondiabetic patients (107/1,541 [6.97%] vs 117/1,500 patients [7.83%]; HR: 0.88; 95% CI: 0.68-1.15; $P = 0.35$), with no heterogeneity at interaction testing ($P_{interaction} = 0.47$; adjusted $P_{interaction} = 0.49$) (**Table 2**). Similarly, MACCEs did not differ in the abbreviated and standard APT groups among diabetic patients (55/754 [7.34%] vs 53/784 [6.79%]; HR: 1.08; 95% CI: 0.74-1.58; $P = 0.69$) and nondiabetic patients (83/1,541 [5.41%] vs 85/1,500 patients [5.69%]; HR: 0.95; 95% CI: 0.70-1.28; $P = 0.73$), with no heterogeneity ($P_{interaction} = 0.59$; adjusted $P_{interaction} = 0.49$) (**Table 2**). MCB was lower with abbreviated APT in nondiabetic patients (95/1,541 [6.25%] vs 139/1,500 patients [9.37%]; HR: 0.65; 95% CI: 0.50-0.85; $P = 0.001$) and diabetic patients (53/754 [7.13%] vs 72/784 patients [9.33%]; HR: 0.75; 95% CI: 0.52-1.06; $P = 0.11$), with no heterogeneity at interaction testing ($P_{interaction} = 0.55$; adjusted $P_{interaction} = 0.29$) (**Table 2**). Abbreviated APT was associated with lower cerebrovascular accident (CVA) rates in diabetic patients (HR: 0.34; 95% CI: 0.13-0.95; $P = 0.04$) because lower rates of stroke and transient ischemic attack, with a consistent trend in nondiabetic patients (HR: 0.68; 95% CI: 0.33-1.43; $P = 0.32$) without significant heterogeneity ($P_{interaction} = 0.28$; adjusted $P_{interaction} = 0.86$). The rate of MI was higher in the abbreviated APT group compared with the standard APT group in diabetic patients (HR: 2.01; 95% CI: 1.05-3.83; $P = 0.03$) but not in nondiabetic patients (HR: 0.92; 95% CI: 0.57-1.47; $P = 0.72$), with borderline significance at interaction testing ($P_{interaction} = 0.06$; adjusted $P_{interaction} = 0.31$). There was no clear evidence of heterogeneity of the treatment effects by diabetes for any of the other secondary endpoints (Supplemental Figure 4). The

TABLE 1 Clinical Outcomes at 11 Months After Randomization in Diabetic vs Nondiabetic Patients

	Diabetics (n = 1,538)	Nondiabetics (n = 3,041)	HR (95% CI)	*P* Value	Adjusted HR (95% CI)[a]	Adjusted *P* Value[a]
NACE	130 (8.50)	224 (7.39)	1.15 (0.93-1.43)	0.19	1.14 (0.79-1.64)	0.48
MACCE	108 (7.06)	168 (5.55)	1.28 (1.00-1.63)	0.05	1.22 (0.79-1.87)	0.37
MCB	125 (8.25)	234 (7.79)	1.06 (0.85-1.32)	0.60	1.16 (0.83-1.61)	0.39
Death	60 (3.92)	96 (3.17)	1.24 (0.90-1.71)	0.19	1.37 (0.79-2.39)	0.26
Cardiovascular death	34 (2.24)	47 (1.56)	1.44 (0.92-2.23)	0.12	1.43 (0.70-2.90)	0.33
Noncardiovascular death	19 (1.26)	38 (1.27)	0.99 (0.57-1.72)	0.98	1.07 (0.35-3.25)	0.91
Cerebrovascular accident	20 (1.32)	29 (0.97)	1.37 (0.78-2.43)	0.27	1.93 (0.61-6.15)	0.26
Stroke[b]	14 (0.93)	21 (0.70)	1.33 (0.67-2.61)	0.41	2.52 (0.68-9.38)	0.17
Ischemic stroke	12 (0.79)	17 (0.57)	1.40 (0.67-2.94)	0.37	2.36 (0.60-9.24)	0.22
Hemorrhagic stroke	2 (0.13)	4 (0.13)	1.00 (0.18-5.43)	1.00	–	–
TIA	6 (0.40)	8 (0.27)	1.49 (0.52-4.30)	0.46	–	–
Myocardial infarction	41 (2.73)	68 (2.27)	1.20 (0.81-1.76)	0.36	0.71 (0.33-1.52)	0.37
Definite or probable ST	9 (0.60)	14 (0.47)	1.28 (0.55-2.95)	0.57	0.12 (0.01-1.99)	0.14
Definite ST	7 (0.46)	11 (0.37)	1.26 (0.49-3.26)	0.63	0.45 (0.01-15.38)	0.66
Probable ST	2 (0.13)	3 (0.10)	1.32 (0.22-7.91)	0.76	–	–
Bleeding (BARC classification)						
Type 1	48 (3.18)	126 (4.19)	0.75 (0.54-1.04)	0.09	0.82 (0.48-1.39)	0.46
Type 2	87 (5.76)	167 (5.57)	1.03 (0.80-1.34)	0.81	1.09 (0.73-1.62)	0.66
Type 3	37 (2.44)	75 (2.50)	0.98 (0.66-1.45)	0.92	1.06 (0.59-1.90)	0.85
Type 3a	18 (1.19)	38 (1.27)	0.94 (0.54-1.65)	0.83	0.87 (0.36-2.11)	0.77
Type 3b	14 (0.93)	27 (0.90)	1.03 (0.54-1.96)	0.93	1.28 (0.54-3.05)	0.57
Type 3c	5 (0.33)	11 (0.37)	0.90 (0.31-2.60)	0.85	0.56 (0.05-6.52)	0.64
Type 4	0 (0.00)	0 (0.00)	–	–	–	–
Type 5	4 (0.27)	6 (0.20)	1.33 (0.37-4.70)	0.66	1.37 (0.41-4.55)	0.74
Type 5a	0 (0.00)	2 (0.07)	0.40 (0.02-8.33)	0.55	–	–
Type 5b	4 (0.27)	4 (0.13)	1.99 (0.50-7.95)	0.33	–	–
Type 3 or 5	41 (2.71)	81 (2.70)	1.00 (0.69-1.46)	0.98	1.10 (0.62-1.94)	0.75

Values are n of first events of each type (Kaplan-Meier failure %); HR (95% CI) from Cox's time-to-first event analyses in the intention-to-treat population, continuity corrected risk ratios (95% CIs) in case of 0 events with the Fisher exact test *P* value, and interaction *P* value testing for the modifying effect of diabetes (yes or no) on the HR scale. [a]Adjusted for the following baseline (age, sex, body mass index, family history of coronary artery disease, arterial hypertension, hyperlipidemia, current smoking, known peripheral/vascular disease, history of heart failure, left ventricular ejection fraction, prior myocardial infarction, prior stroke, prior coronary artery bypass grafting, prior bleeding, known chronic pulmonary disease, chronic renal failure, atrial fibrillation, known active cancer, known hematologic or coagulation disorders, chronic treatment with steroids or nonsteroidal anti-inflammatory drugs, clinical indication for oral anticoagulation, and PRECISE DAPT score) and procedural (total number of vessels treated per patient ≥2, treated vessel: left main, treated vessel: left anterior descending artery, total stented lesions per patient ≥3, total stent length per patient, and any bifurcation or trifurcation stenting) features. [b]Includes undetermined strokes.

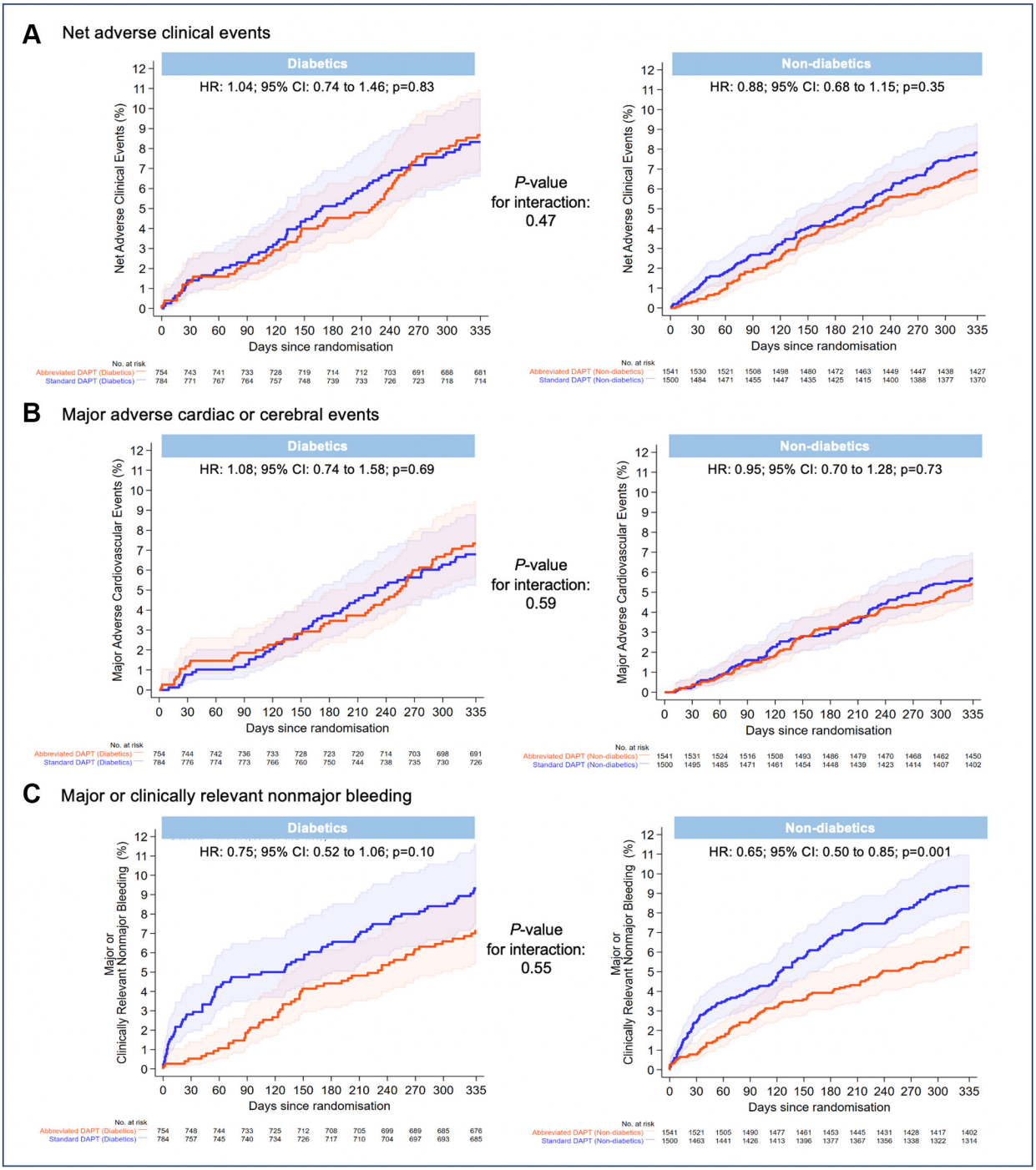
BARC = Bleeding Academic Research Consortium; MACCE = major adverse cardiac and cerebral event(s); MCB = major or clinically relevant nonmajor bleeding; NACE = net adverse clinical event(s); ST = stent thrombosis; TIA = transient ischemic attack.

rates of definite or probable ST in the diabetic population were similarly low with abbreviated or standard APT (HR: 2.08; 95% CI: 0.52-8.30; $P = 0.30$) (**Table 2**, Supplemental Figure 5). MCB reduction with abbreviated DAPT was mainly driven by lower rates of Bleeding Academic Research Consortium type 2 bleeding, which were numerically and significantly lower in diabetic (HR: 0.68; 95% CI: 0.45-1.05; $P = 0.08$) and nondiabetic patients (HR: 0.64; 95% CI: 0.47-0.88; $P = 0.005$; $P_{\text{interaction}} = 0.82$; adjusted $P_{\text{interaction}} = 0.29$), respectively (**Table 2**).

ADDITIONAL ANALYSES. Among diabetic and nondiabetic patients with a clinical indication for OAC (**Figure 3**, Supplemental Table 7), NACEs, MACCEs, and MCB did not differ with abbreviated vs standard APT. Among diabetic and nondiabetic patients without a clinical indication for OAC (**Figure 3**, Supplemental Table 8), NACEs and MACCEs did not differ, and MCB was consistently reduced in diabetic and nondiabetic patients (HR: 0.51; 95% CI, 0.30-0.86; $P = 0.012$ and HR: 0.57; 95% CI: 0.39-0.83; $P = 0.003$; $P_{\text{interaction}} = 0.74$; adjusted $P_{\text{interaction}} = 0.87$) with abbreviated vs standard APT regimens.

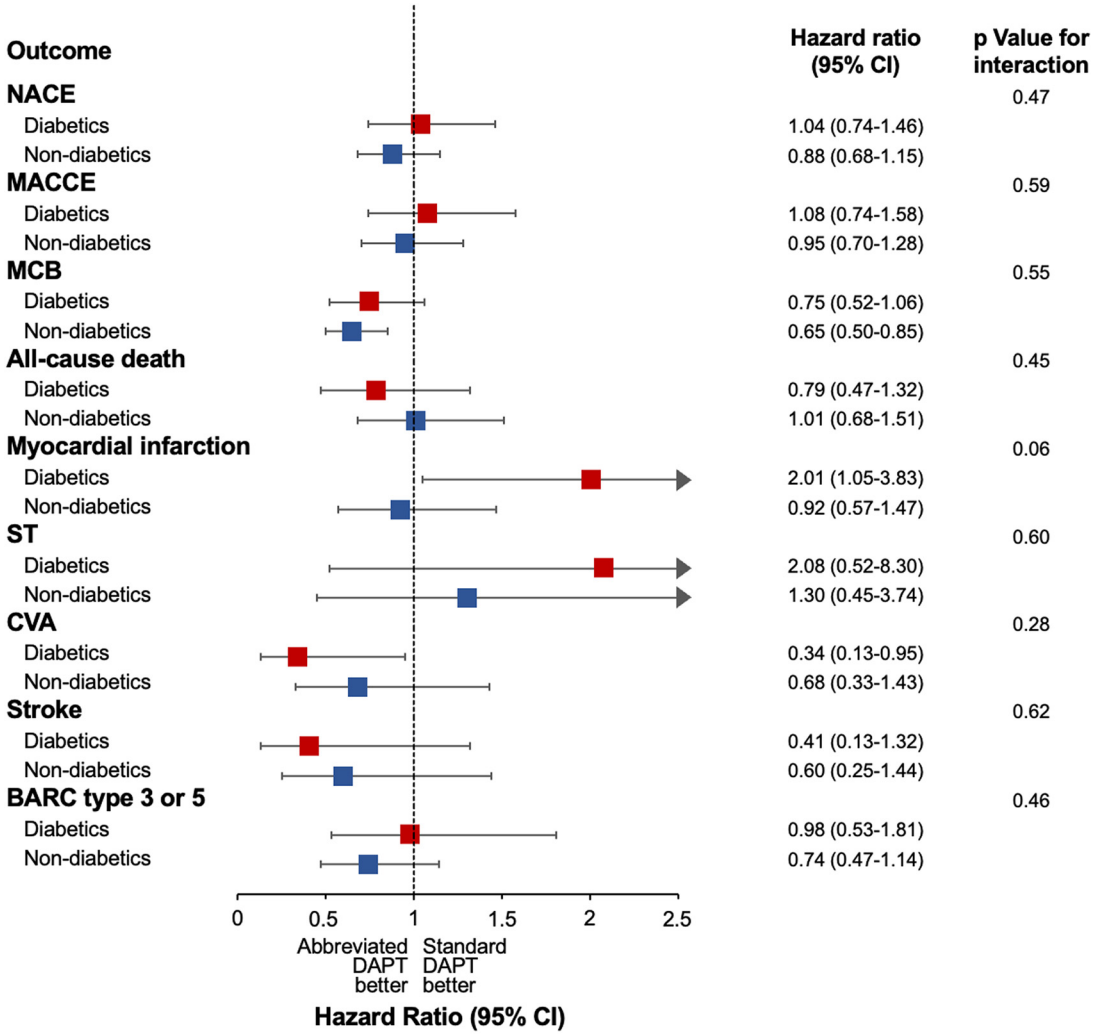
The treatment effect for MI was consistent across insulin dependency strata in the overall population and in male and female patients, separately analyzed, with no significant heterogeneity at interaction testing (Supplemental Figure 6). There were 13 more primary MI events in diabetic patients with abbreviated compared with standard APT, of which the majority (n = 9 [69%]) were classified as type 4C (in-stent restenosis related) or 2 (spontaneous) (Supplemental Table 9). The apparent excess of MI in diabetic patients with abbreviated compared with

FIGURE 1 **Net Adverse Clinical Events, Major Adverse Cardiac or Cerebral Events, and Major or Clinically Relevant Nonmajor Bleeding**



Kaplan-Meier curves for (A) net adverse clinical events, (B) major adverse cardiac or cerebral events, and (C) and major or clinically relevant nonmajor bleeding. DAPT = dual antiplatelet therapy.

FIGURE 2 Main Outcomes of Abbreviated vs Standard APT in Diabetic and Nondiabetic Patients



Abbreviated and standard antiplatelet therapy (APT) were compared based on diabetes status, with HRs and 95% CIs for the 3 coprimary outcomes and their components (all-cause death, myocardial infarction, stroke, and Bleeding Academic Research Consortium [BARC] type 3 or 5). CVA = cerebrovascular accident; DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebral event(s); MCB = major or clinically relevant nonmajor bleeding; NACE = net adverse clinical event(s); ST = stent thrombosis.

standard APT accrued mainly from male patients (22/539 [4.17%] vs 8/523 patients [1.56%]; HR: 2.69; 95% CI: 1.20-6.05). No significant heterogeneity of the treatment effect for CVA by sex was detected across DM strata (Supplemental Figure 7). Abbreviated compared with standard APT was associated with a numeric reduction of CVA in diabetic (HR: 0.24; 95% CI: 0.05-1.14) and nondiabetic (HR: 0.82; 95% CI: 0.34-1.98) 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 regimen among HBR patients. Patients with DM incurred a 28% higher rate of MACCEs and similar NACE and 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 3 coprimary outcomes, suggesting that abbreviated APT was consistently associated with similar NACE and MACCE rates and reduced MCB rates compared with standard APT in both diabetic and nondiabetic patients (**Central Illustration**). MCB was significantly reduced in nondiabetic patients, whereas in diabetic patients the upper limit of the 95% CI slightly exceeds the null. However, we observed no significant heterogeneity of the treatment effect at interaction testing for MCB, suggesting a consistent reduction of bleeding with abbreviated compared with standard APT in both diabetic and nondiabetic patients.

The observation of similar NACE and MACCE rates and a consistent bleeding reduction with abbreviated compared with standard APT in both diabetic and nondiabetic patients suggests 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.[8-11,21] 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.[11,22,23] DM is acknowledged as an ischemic risk enhancer across European Society of Cardiology guidelines on acute[22] and chronic coronary syndrome[24] and may or should justify a second antithrombotic agent in patients without or with complex CAD, respectively. However, these recommendations apply to patients without HBR.

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. Conversely, CVA rates were nominally lower with abbreviated compared with standard APT among HBR patients with DM, driven by a numerically lower rate of strokes (both ischemic and hemorrhagic events) and transient ischemic attack. A relevant finding was the absence of clear evidence of heterogeneity between the 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 vs prolonged DAPT in patients with and without diabetes. In an individual patient data meta-analysis of 6 trials, including 11,473 patients randomized to 6- or 12-month DAPT after drug-eluting stent implantation, the presence of DM was an independent predictor of major adverse clinical events (MACEs) after PCI;[25] however, compared with short-term DAPT, long-term DAPT did not reduce the risk of MACEs but did increase the risk of bleeding among PCI patients with and without diabetes.[25] The results of our study are consistent with those findings and expand their application to an HBR population.

In the DAPT (Dual Antiplatelet Therapy) trial, continued thienopyridine beyond 12 months reduced the MACCE rate among nondiabetic (n = 6,924; HR: 0.59; 95% CI: 0.46-0.74) but not diabetic (n = 3,037; HR: 0.95; 95% CI: 0.72-1.25) patients, with significant treatment by DM interaction ($P_{\text{interaction}} = 0.01$).[26]

In the PEGASUS (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) trial, patients with a history of prior MI (1-3 years before) and at least 1 additional atherothrombotic risk factor (including DM) were eligible for inclusion.[27] Patients with DM had higher rates of ischemic events compared with nondiabetic patients. In this trial, the risk of MACEs (the composite of cardiovascular death, MI, or stroke) in the placebo arm was 11.60% among diabetic patients vs 7.83% in those without diabetes (adjusted HR: 1.45; 95% CI: 1.22-1.73; $P < 0.001$).[27] The relative risk reduction in MACEs for the pooled ticagrelor doses vs placebo was consistent in patients with (n = 6,806; HR: 0.84; 95% CI: 0.72-0.99; $P = 0.035$) and without DM (n = 14,355; HR: 0.84; 95% CI: 0.74-0.96; $P = 0.013$), without significant heterogeneity of the treatment effect at interaction testing ($P_{\text{interaction}} = 0.99$).[27] The absolute risk reduction of MACEs with aspirin and ticagrelor compared with aspirin alone was also similar in patients with and without DM, as was the risk of bleeding. TIMI major bleeding was significantly increased in diabetic patients treated with ticagrelor (2.56% vs 0.98%; HR: 2.56; 95% CI: 1.52-4.33; $P = 0.0004$), at a similar magnitude to what was detected in nondiabetic patients (2.39% in pooled ticagrelor vs 1.09% in placebo; HR: 2.47; 95% CI: 1.73-3.53; $P < 0.0001$; $P_{\text{interaction}} = 0.89$).[27] Our results extend these findings to HBR patients and suggest that DM should not be regarded as a treatment

TABLE 2 Clinical Outcomes at 11 Months After Randomization in Diabetic and Nondiabetic Patients Randomized to Abbreviated or Standard DAPT

	Diabetics				
	Abbreviated DAPT (n = 754)	Standard DAPT (n = 784)	HR (95% CI)	*P* Value	Com-Nogue Risk Difference (95% CI)
NACE	65 (8.67)	65 (8.33)	1.04 (0.74-1.46)	0.83	0.35 (−2.45 to 3.14)
MACCE	55 (7.34)	53 (6.79)	1.08 (0.74-1.58)	0.69	0.55 (−2.02 to 3.12)
MCB	53 (7.13)	72 (9.33)	0.75 (0.52-1.06)	0.11	−2.19 (−4.96 to 0.57)
Death	26 (3.47)	34 (4.36)	0.79 (0.47-1.32)	0.37	−0.88 (−2.83 to 1.06)
Cardiovascular death	14 (1.88)	20 (2.59)	0.72 (0.37-1.43)	0.35	−0.71 (−2.20 to 0.78)
Noncardiovascular death	9 (1.22)	10 (1.30)	0.93 (0.38-2.29)	0.88	−0.08 (−1.21 to 1.05)
Undetermined death	3 (0.41)	4 (0.52)	0.78 (0.17-3.47)	0.74	−0.11 (−0.80 to 0.57)
Cerebrovascular Accident	5 (0.67)	15 (1.96)	0.34 (0.13-0.95)	0.04	−1.29 (−2.43 to −0.15)
Stroke[b]	4 (0.53)	10 (1.31)	0.41 (0.13-1.32)	0.14	−0.77 (−1.73 to 0.19)
Ischemic stroke	4 (0.53)	8 (1.05)	0.52 (0.16-1.72)	0.28	−0.51 (−1.40 to 0.38)
Hemorrhagic stroke	0 (0.00)	2 (0.26)	0.21 (0.01-4.37)	0.50	−0.26 (−0.63 to 0.10)
TIA	1 (0.13)	5 (0.65)	0.21 (0.02-1.77)	0.15	−0.52 (−1.14 to 0.11)
Myocardial infarction	27 (3.66)	14 (1.83)	2.01 (1.05-3.83)	0.03	1.83 (0.18-3.48)
Definite or probable ST	6 (0.81)	3 (0.39)	2.08 (0.52-8.30)	0.30	0.42 (−0.36 to 1.20)
Definite ST	5 (0.68)	2 (0.26)	2.59 (0.50-13.37)	0.26	0.42 (−0.28 to 1.11)
Probable ST	1 (0.13)	1 (0.13)	1.04 (0.06-16.58)	0.98	0.01 (−0.36 to 0.37)
Bleeding (BARC classification)					
Type 1	21 (2.84)	27 (3.51)	0.80 (0.45-1.41)	0.44	−0.67 (−2.44 to 1.10)
Type 2	35 (4.72)	52 (6.76)	0.68 (0.45-1.05)	0.08	−2.04 (−4.38 to 0.31)
Type 3	19 (2.56)	18 (2.33)	1.09 (0.57-2.07)	0.80	0.23 (−1.32 to 1.79)
Type 3a	8 (1.08)	10 (1.29)	0.82 (0.33-2.09)	0.68	−0.20 (−1.29 to 0.88)
Type 3b	8 (1.08)	6 (0.78)	1.38 (0.48-3.97)	0.55	0.30 (−0.67 to 1.27)
Type 3c	3 (0.40)	2 (0.26)	1.55 (0.26-9.29)	0.63	0.14 (−0.44 to 0.72)
Type 4	0 (0.00)	0 (0.00)			
Type 5	1 (0.14)	3 (0.39)	0.34 (0.04-3.31)	0.36	−0.26 (−0.78 to 0.26)
Type 5a	0 (0.00)	0 (0.00)			
Type 5b	1 (0.14)	3 (0.39)	0.34 (0.04-3.31)	0.36	−0.26 (−0.78 to 0.26)
Type 3 or 5	20 (2.70)	21 (2.72)	0.98 (0.53-1.81)	0.95	−0.02 (−1.66 to 1.62)

Values are n of first events of each type (Kaplan-Meier failure %); HR (95% CI) from Cox's time-to-first event analyses in the intention-to-treat population, continuity corrected risk ratios (95% CIs) in case of 0 events with the Fisher exact test *P* value, and interaction *P* value testing for the modifying effect of diabetes (yes or no) on the HR scale. aAdjusted for the following baseline (age, sex, body mass index, family history of coronary artery disease, arterial hypertension, hyperlipidemia, current smoking, known peripheral/vascular disease, history of heart failure, left ventricular ejection fraction, prior myocardial infarction, prior stroke, prior coronary artery bypass grafting, prior bleeding, known chronic pulmonary disease, chronic renal failure, atrial fibrillation, known active cancer, known hematologic or coagulation disorders, chronic treatment with steroids or nonsteroidal anti-inflammatory drugs, clinical indication for oral anticoagulation, and PRECISE DAPT score) and procedural (total number of vessels treated per patient ≥2, treated vessel: left main, treated vessel: left anterior descending artery, total stented lesions per patient ≥3, total stent length per patient, and any bifurcation or trifurcation stenting) features. bIncludes undetermined strokes.

Abbreviations as in Table 1.

Continued on the next page

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 nondiabetic patients. A subgroup analysis of the GLOBAL-LEADERS study showed consistent treatment effects in patients with or without DM who underwent 23 months of ticagrelor monotherapy after 1 month of DAPT compared with 12 months of DAPT followed by aspirin monotherapy.[28] Our results are also in line with a subanalysis from the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial,[29] 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 2 groups (3.1% with ticagrelor monotherapy vs 4.1% with ticagrelor plus aspirin), although it was much higher than the 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 vs 1 month in MASTER DAPT), and the type of SAPT (ticagrelor monotherapy in TWILIGHT vs 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 6 trials,

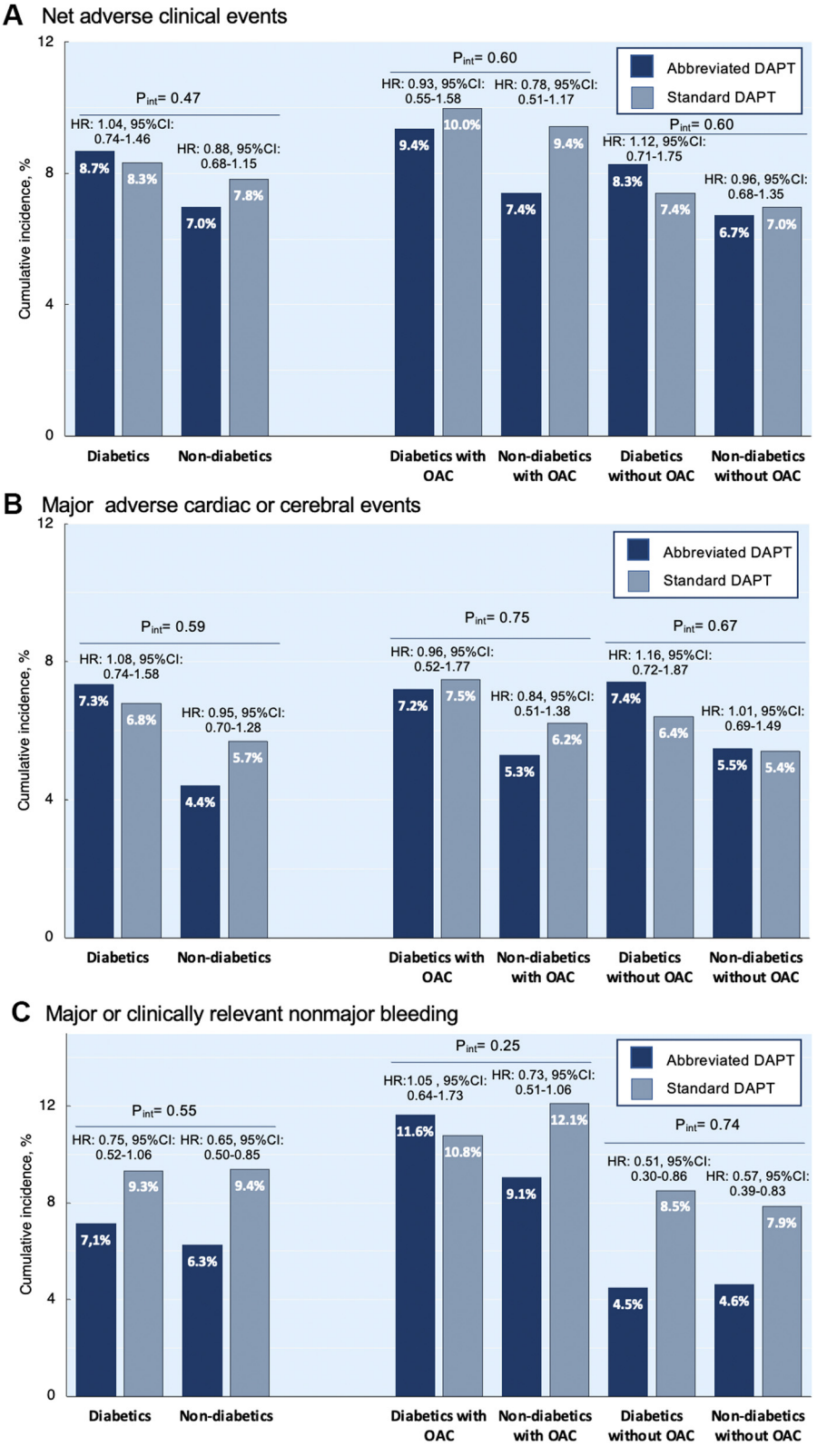
TABLE 2 Continued

Nondiabetics						
Abbreviated DAPT (n = 1,541)	Standard DAPT (n = 1,500)	HR (95% CI)	*P* Value	Com-Nogue Risk Difference (95% CI)	Interaction *P* Value	Adjusted Interaction *P* Value[a]
107 (6.97)	117 (7.83)	0.88 (0.68-1.15)	0.35	−0.87 (−2.73 to 1.00)	0.47	0.49
83 (5.41)	85 (5.69)	0.95 (0.70-1.28)	0.73	−0.29 (−1.92 to 1.34)	0.59	0.49
95 (6.25)	139 (9.37)	0.65 (0.50-0.85)	0.001	−3.13 (−5.04 to −1.21)	0.55	0.29
49 (3.19)	47 (3.15)	1.01 (0.68-1.51)	0.95	0.04 (−1.21 to 1.29)	0.45	0.83
23 (1.51)	24 (1.62)	0.93 (0.53-1.65)	0.81	−0.11 (−0.99 to 0.78)	0.58	0.06
20 (1.32)	18 (1.22)	1.08 (0.57-2.04)	0.81	0.10 (−0.71 to 0.90)	0.79	0.34
6 (0.40)	5 (0.34)	1.17 (0.36-3.82)	0.80	0.05 (−0.38 to 0.49)	0.68	–
12 (0.80)	17 (1.15)	0.68 (0.33-1.43)	0.32	−0.36 (−1.06 to 0.35)	0.28	0.86
8 (0.53)	13 (0.88)	0.60 (0.25-1.44)	0.25	−0.35 (−0.95 to 0.25)	0.62	0.69
7 (0.46)	10 (0.68)	0.68 (0.26-1.79)	0.43	−0.22 (−0.76 to 0.32)	0.73	0.60
1 (0.07)	3 (0.20)	0.32 (0.03-3.11)	0.33	−0.14 (−0.40 to 0.13)		–
4 (0.27)	4 (0.27)	0.97 (0.24-3.88)	0.97	0.00 (−0.38 to 0.37)	0.24	–
33 (2.18)	35 (2.37)	0.92 (0.57-1.47)	0.72	−0.20 (−1.26 to 0.87)	0.06	0.31
8 (0.53)	6 (0.41)	1.30 (0.45-3.74)	0.63	0.12 (−0.37 to 0.61)	0.60	–
6 (0.40)	5 (0.34)	1.17 (0.36-3.83)	0.80	0.06 (−0.38 to 0.49)	0.44	–
2 (0.13)	1 (0.07)	1.95 (0.18-21.46)	0.59	0.06 (−0.16 to 0.29)	0.74	–
44 (2.89)	82 (5.53)	0.52 (0.36-0.74)	<0.001	−2.64 (−4.08 to −1.21)	0.20	0.60
67 (4.41)	100 (6.76)	0.64 (0.47-0.88)	0.01	−2.35 (−4.00 to −0.71)	0.82	0.29
34 (2.24)	41 (2.77)	0.80 (0.51-1.26)	0.34	−0.53 (−1.65 to 0.59)	0.45	0.60
18 (1.19)	20 (1.35)	0.87 (0.46-1.65)	0.68	−0.17 (−0.97 to 0.63)	0.92	–
13 (0.86)	14 (0.95)	0.90 (0.42-1.92)	0.79	−0.09 (−0.77 to 0.59)	0.52	–
4 (0.27)	7 (0.47)	0.56 (0.16-1.90)	0.35	−0.21 (−0.64 to 0.23)	0.35	–
0 (0.00)	0 (0.00)					
1 (0.07)	5 (0.34)	0.19 (0.02-1.66)	0.14	−0.27 (−0.60 to 0.05)	0.72	0.49
0 (0.00)	2 (0.14)	0.19 (0.01-3.95)	0.24	−0.14 (−0.32 to 0.05)	1.00	–
1 (0.07)	3 (0.20)	0.32 (0.03-3.11)	0.33	−0.14 (−0.40 to 0.13)	0.97	–
35 (2.31)	46 (3.11)	0.74 (0.47-1.14)	0.17	−0.80 (−1.96 to 0.36)	0.46	0.49

$P2Y_{12}$ inhibitor monotherapy (ticagrelor 77%, clopidogrel 22%, and prasugrel 1%) compared with 12-month DAPT was associated with lower bleeding and similar death, MI, and stroke rates.[30] Subgroup analyses demonstrated a reduction in major adverse cardiovascular events with $P2Y_{12}$ inhibitor monotherapy in diabetic patients (HR: 0.70; 95% CI: 0.63-0.99) but not in nondiabetic subjects (HR: 1.00; 95% CI: 0.81-1.24) with no significant heterogeneity of treatment effect at interaction testing ($P_{interaction}$ = 0.10).[30] Therefore, prior evidence concurs with our present finding suggesting that DM, albeit potentially associated with a greater risk of a fatal or nonfatal composite endpoint, should not per se drive the decision making on DAPT duration.

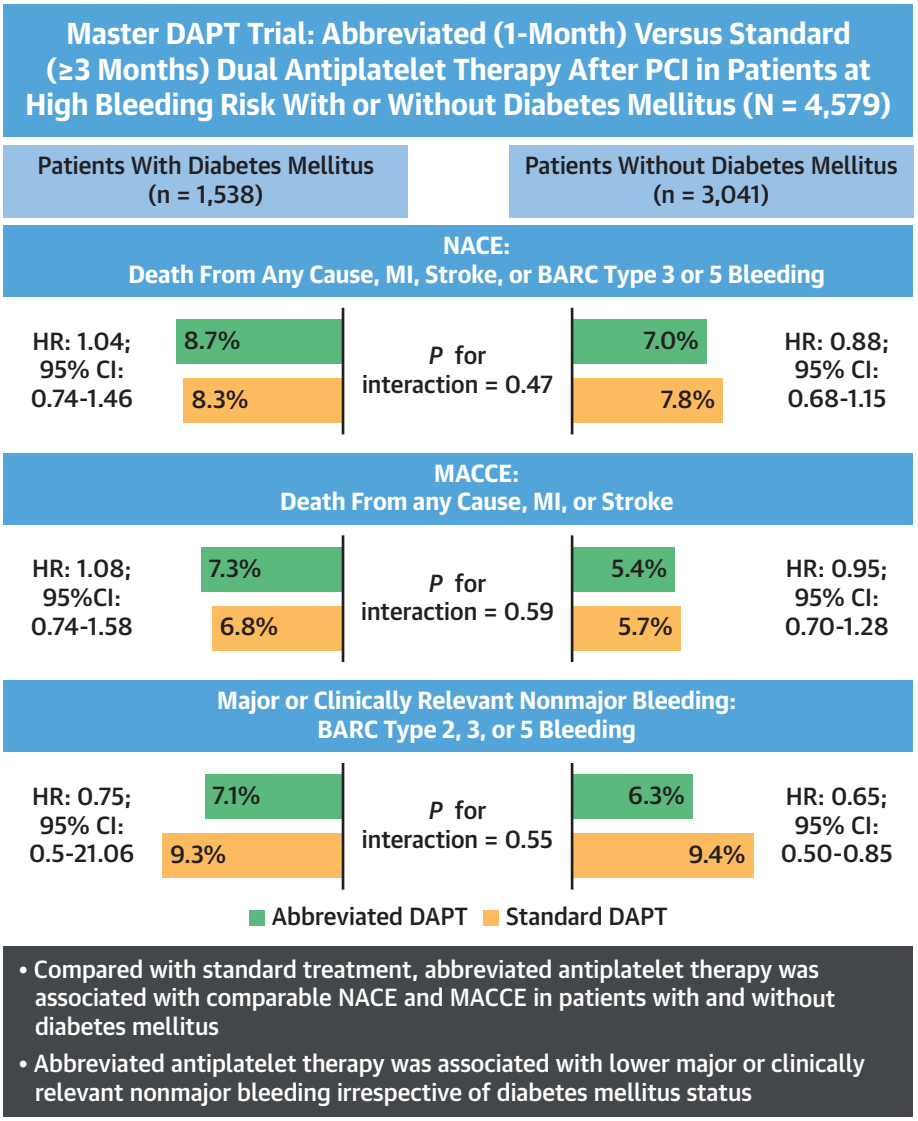
STUDY LIMITATIONS. First, MASTER DAPT was powered to assess the noninferiority of NACEs and MACCEs in the overall study population, whereas no noninferiority claim is possible when interpreting subgroup analyses, for which the study is inherently underpowered. Therefore, as all subgroup analyses, these results should be considered hypothesis generating with respect to the risks and benefits of an abbreviated vs 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. These results could not be extended to patients with in-stent restenosis or stent thrombosis who were ineligible for trial participation. Finally, the duration of DAPT in both arms was longer than currently recommended in patients taking OAC.[22,31,32] However, a very short duration of triple antithrombotic therapy is associated with higher rates of ischemic events compared with longer treatment.[33]

FIGURE 3 Interaction Between Diabetes Mellitus and DAPT on Coprimary 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 oral anticoagulation (OAC), and the y-axis shows event rates of the coprimary efficacy outcomes. (A) NACEs, (B) MACCEs, and (C) MCB. Abbreviations as in Figure 2.

CENTRAL ILLUSTRATION DAPT Duration and Outcomes



Roffi M, et al. JACC Cardiovasc Interv. 2024;17(22):2664–2677.

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac or cerebral event(s); MASTER DAPT = Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With a Abbreviated Versus Prolonged DAPT Regimen; NACE = net adverse clinical event(s); MI = myocardial infarction; PCI = percutaneous coronary intervention.

CONCLUSIONS

In this prespecified analysis of the MASTER DAPT trial, HBR patients with DM experienced higher MACCEs and similar NACEs and bleeding rates compared with nondiabetic subjects. MACCE and NACE rates were similar and bleeding rates were lower with abbreviated APT in patients with or without diabetes. Therefore, diabetes status did not modify the treatment effects of abbreviated vs standard APT in HBR patients after biodegradable polymer sirolimus-eluting coronary stent implantation.

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PERSPECTIVES

WHAT IS KNOWN? Diabetic patients at HBR have higher risks of ischemic events and similar bleeding risk than nondiabetic subjects.

WHAT IS NEW? Among HBR patients undergoing coronary revascularization, an abbreviated DAPT is associated with comparable MACCEs and NACEs and consistently reduced bleeding compared with treatment continuation for at least 2 additional months irrespective of diabetes status.

WHAT IS NEXT? Future studies should investigate the safety and efficacy of shorter than 1-month DAPT in HBR patients with diabetes undergoing revascularization in the setting of acute coronary syndrome.

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KEY WORDS diabetes mellitus, dual antiplatelet therapy, high bleeding risk, percutaneous coronary intervention

APPENDIX For an expanded Methods section, a list of investigators, and supplemental tables and figures, please see the online version of this paper.