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Optimal Duration of Dual Antiplatelet Therapy after Second-Generation Drug-Eluting Stent Implantation in Patients with Diabetes: the SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy)-diabetes substudy

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ABSTRACT

BACKGROUND/OBJECTIVES The randomized SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) trial showed the non-inferiority of 6 vs. 12-month DAPT after percutaneous coronary intervention (PCI) with second-generation DES in a low-risk population. Nevertheless, diabetes mellitus (DM) remained a major predictor of adverse cardiovascular events. We aimed to assess the interaction between DAPT duration and outcome in DM patients.

METHODS All diabetic patients included in the SECURITY trial treated by second-generation DES PCI were analyzed. The primary endpoint was a composite of cardiac death, myocardial infarction (MI), stroke, definite or probable stent thrombosis (ST), or Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding at 12 months. The main secondary endpoint was a composite of cardiac death, MI, stroke, definite or probable ST, or BARC type 2, 3, or 5 bleeding at 24 months.

RESULTS Four hundred-twenty nine DM patients received either 6 (n=206) or 12 (n=223) months of DAPT. The primary endpoint occurred in 3.9% and 5.4% of patients in the 6 and 12-month DAPT group, respectively (log-rank test $p=0.83$). Similarly, no statistically significant difference in the secondary endpoint was observed between the two study groups (5.4% vs. 7.6%, $p=0.620$). Stent thrombosis rate was low irrespective of DAPT duration at both 12 (0.5% vs. 0.4%; $p=0.804$) and between 12 and 24 months of follow-up (0.5% vs. 0%, $p=0.291$). At multivariable analysis, female gender (HR: 3.42; 95% CI 1.32-8.85; $p=0.011$ and HR 2.28; 95% CI 1.09-4.75; $p=0.027$) and insulin-treated diabetes mellitus (HR: 2.62; 95% CI 1.15-6.75; $p=0.004$ and HR: 2.23; 95% CI 1.09-6.33; $p=0.003$) were independent predictors of both primary and secondary endpoint.

CONCLUSIONS In diabetic patients treated by second-generation DES PCI, we failed to find any additional benefit of prolonging DAPT beyond 6 months, regardless of insulin-requiring status.

BACKGROUND/OBJECTIVES

Dual antiplatelet therapy (DAPT) is the cornerstone of the prevention of stent thrombosis (ST) after PCI, even though its optimal duration has yet to be established. Moving from first to second-generation DES, the recent European Society of Cardiology (ESC) guidelines on myocardial revascularization suggested a DAPT duration of at least 6 months[1]. In the randomized, multicenter SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six-Versus Twelve-Month Dual Antiplatelet Therapy) trial[2] enrolling patients with stable or unstable angina undergoing second-generation DES implantation we found that 6-month was non-inferior to 12-month DAPT in terms of net clinical adverse (including ischemic and hemorrhagic) events. Nevertheless, in this study DM remained an independent predictor of worse outcome.

In the pre-specified analysis of the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) trial diabetic patients had an higher rate of target vessel failure and stent thrombosis (ST) with shorter (6-months) DAPT[3]. These findings have raised the question whether diabetic patients might need longer DAPT than non-diabetic.

Therefore, we aimed to explore the impact of 6 vs. 12 month DAPT regimen on both ischemic and bleeding risk in DM patients treated with second-generation DES and enrolled in the SECURITY trial.

METHODS

STUDY DESIGN AND POPULATION. All diabetic patients enrolled in the SECURITY trial (NCT00944333) were analyzed. The latter was a prospective, randomized, non-inferiority, investigator-driven, multicenter, international study, conducted between July 2009 and June 2014 enrolling patients with stable or unstable angina treated with at least 1 second-generation DES. Details about inclusion and exclusion criteria were reported previously[2]. Diagnostic criteria for DM were fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or oral glucose tolerance test with 2-h plasma glucose ≥ 11.1 mmol/l (200 mg/dl).

TREATMENT PROTOCOL AND CLINICAL FOLLOW-UP. All patients were randomized to receive 6 versus 12 months of DAPT. Randomization was performed by web-based case report, according to a 1:1 scheme, randomized with blocks of equal size. Second-generation DES used were the Endeavor Resolute (Medtronic, Minneapolis, Minnesota), Xience (Abbott Vascular, Abbott Park, Illinois), Promus (Boston Scientific, Natick, Massachusetts), Nobori (Terumo Corporation, Tokyo, Japan), and Biomatrix (Biosensors Europe, Morges, Switzerland).

Clopidogrel 75 mg per day for at least 3 days before the procedure or a pre-procedural loading dose of a minimum of 300 mg of clopidogrel was administered to patients not on chronic clopidogrel therapy. In the post-procedure period, 75 mg of clopidogrel for 6 or 12 months, according to randomization allocation, were administered. Conversely, post-procedure use of aspirin was prescribed indefinitely. Following their introduction to the market, the protocol was amended to allow the new antiplatelet compounds prasugrel and ticagrelor.

Follow-up assessments were done at 30 ± 5 days, at 180 ± 14 days (6 months), at 365 days (-14 days/ $+30$ days), and at 730 days (-14 days/ $+30$ days), by means of telephone call or outpatient clinical evaluation. Angiographic follow-up was not mandatory in the protocol.

An independent clinical research organization (Mediolanum Cardio Research, Milan, Italy) performed data monitoring. Data collection was done using electronic case report forms, which were reviewed for accuracy and compared with source documents during onsite monitoring visits

by Mediolanum Cardio Research. All events were evaluated and assigned by an independent clinical event committee composed of interventional cardiologists not participating in the study.

STUDY ENDPOINTS. The SECURITY-diabetes substudy's endpoints were the same of the SECURITY trial. Briefly, primary endpoint was a composite of cardiac death, MI, stroke, definite or probable ST⁶, or Bleeding Academic Research Consortium (BARC) criteria type 3 or 5 bleeding[4] at 12 months. Secondary endpoints were: 1) a composite of cardiac death, spontaneous MI, stroke, definite or probable ST, or BARC type 2, 3, or 5 bleeding at 12 and 24 months; 2) urgent target vessel revascularization (coronary artery bypass surgery or PCI because of acute cardiac ischemia); 3) all-cause mortality at 30 days and 6, 12, and 24 months.

STATISTICAL ANALYSIS. Quantitative variables were summarized as mean $\pm$ standard deviation, categorical ones with count and percentage in each category. Patient's quantitative characteristics were compared between the DAPT groups with unpaired Student's t test or Mann-Whitney test, for categorical characteristics chi-square or Fisher's exact test were used. Survival curves were estimated by the Kaplan-Meier method and compared using log-rank test.

All patient's characteristics statistically significant in the univariable analysis at the bilateral 5% level were included in a multivariable Cox proportional hazard regression model for the primary and secondary end-points.

The results of the analyses are reported as bilateral p-values and bilateral 90% confidence interval (90% CI) for the difference in the cumulative incidence of the specific end-point. An independent statistician (P.T.) performed all analyses using R version 3.1.2.

RESULTS

Out of 1399 patients, 429 (31%) DM subjects aged 66.1 ± 9.6 years were included in our sub-analysis. The flow algorithm of our study population is shown in Figure 1. Baseline clinical, angiographic and procedural characteristics were well balanced between the two study groups (Tables 1-3). Two hundred and six (48%) patients had a previous cardiovascular event and 283 (66%) had stable angina. Multivessel CAD was present in 219 (51%) patients, with left anterior descending coronary artery involved in 40% of the cases. Radial access was the preferred approach in 71%. With regard to second-generation DES implanted, 294 (41%) received an Endeavor Resolute, 187 (25.9%) a Nobori, 90 (12.4%) a Promus, 56 (7.8%) a Xience, and 47 (6.5%) a Biomatrix stent. The discharge DAPT therapy was aspirin and clopidogrel in all but one case. Clinical follow-up at 12 and 24 months were successfully performed in 390 (91%) and 348 (81%) patients, respectively. Mean study duration was 18.6 ± 9.5 and 17.1 ± 10.0 months for the two study groups. Adherence to DAPT at 6 months was 99% in both groups; at 12 months 28% vs. 97% in the 6- and 12-month group, respectively. At 24 months, 98% of patients in both groups were on aspirin. Clinical outcomes are reported in Table 4. The primary composite endpoint was observed in 3.9% vs. 5.4% in the 6- and 12-month DAPT group, respectively (log-rank $p=0.83$). Figure 2 shows estimates of the probability of occurrence of the primary endpoint in the study groups at 12 months. The secondary composite endpoint at 12 months and between 12 and 24 months was not different between the two DAPT groups (4.4% vs. 6.3%, $p=0.912$; and 1.5% vs. 2.2%, $p=0.620$). Figure 3 shows estimates of the probability of occurrence of the secondary endpoint in the study groups. Individual components of the primary and secondary endpoints are reported in Table 4. To note, we found only one case of ST beyond the DAPT duration period. At 12 months, bleeding events were as low as 1.0 vs. 1.8% in 6 vs. 12-month DAPT group, respectively. Subgroup analyses for the occurrence of the primary and secondary endpoint are shown in Figure 4a and 4b. To note, at multivariable analysis, predictors of the primary endpoint at 12 months remained female gender (HR: 3.42; 95% CI 1.32-8.85; $p=0.011$) and insulin-treated diabetes

mellitus (HR: 2.62; 95% CI 1.15-6.75; $p=0.004$). At 24 months, female gender (HR 2.28; 95% CI 1.09-4.75; $p=0.027$) and insulin-treated diabetes mellitus (HR: 2.23; 95% CI 1.09-6.33; $p=0.003$) were confirmed as predictors also of the secondary composite endpoint. DAPT duration was not an independent predictor of the primary (HR: 1.33; 95% CI 0.51-3.43; $p=0.559$) or the secondary (HR: 1.50; 95% CI 0.71-3.14; $p=0.283$) endpoint. The Kaplan Meier estimates showing the interplay between insulin-requiring status and DAPT duration are shown in Figure 5a and 5b. Insulin-treated patients had a statistically significant higher rate of events at 24 months, irrespective of DAPT duration. We failed to find any significant impact of stent type on outcome, regardless of DAPT duration (HR 0.72, $p=0.50$ at 12 months; HR 0.81, $p=0.57$ at 24 months).

DISCUSSION

The main findings of the current sub-analysis of the SECURITY trial on the interplay between DAPT duration and outcome in DM patients treated by second-generation DES PCI are: 1) A DAPT regimen prolonged beyond 6-month did not offer any additional benefit on both ischemic and bleeding events; 2) insulin-requiring status remained the major predictor of adverse events during follow-up, irrespective of DAPT duration.

Patients with DM have more accelerated, diffuse and complex atherosclerotic coronary artery disease (CAD), as well as higher rates of restenosis and ST after PCI with DES. As such, they carry a higher risk of both stent- and patient-related adverse events after PCI[5-7]. DAPT after DES implantation is used to reduce the risk for thrombotic events weeks to months after PCI. The recommendation for prolonged (12-month) DAPT in patients with stable CAD treated by PCI comes from studies using first-generation DES. In a recent meta-analysis short term DAPT had overall lower rates of bleeding, but higher rates of stent thrombosis compared with long-term DAPT; interestingly, the latter effect was significantly attenuated with the use of second-generation DES[8]. In fact, the use of second-generation DES has shown promising results in terms of target vessel revascularization, target lesion revascularization and ST, when compared to first-generation DES also in DM patients[9]. Another patient-level, network meta-analysis including mainly stable patients treated with both first and second-generation DES confirmed the absence of any significant interaction between DAPT duration, DM status and outcome[10]. In the recent DAPT trial [11] although patients' selection and DAPT duration were different from our study, DM patients treated by first and second-generation DES did not seem to gain any benefit from prolonged (>12-month) DAPT in terms of MACE reduction, because of increased bleeding complications. Our study is the first to prospectively explore the interplay between DAPT duration and the outcome of DM patients treated by PCI with exclusive use of second-generation DES. By our data, diabetic patients showed a comparable adverse cardiovascular events rate to that observed in the non-diabetic population enrolled in the SECURITY trial either at 6 months (4.8 DM vs. 3.9% non-DM, $p=0.7$) or 12 months

(3.0 DM vs. 5.4% non-DM, $p=0.14$). Thus, we confirmed and extended the absence of significant interaction between DAPT duration and outcome in DM patients treated by second-generation DES[12]. Our diabetic patients carried a very low rate of ST (0.4% at 12-month) that was lower than that reported by others [3, 13, 14]. In the shorter DAPT group only one ST was observed in the first 30 days while in DAPT, no ST was observed instead between 6 and 12 months of follow-up. Beyond the use of second generation DES in all patients, these results might be related to the fact that our patients were at lower clinical risk compared to other studies[15]; in fact, 2/3 of our patients had stable CAD, with low rate of complex lesions, and no one had chronic kidney disease (creatinine $>2\text{mg/dL}$).

Additionally, the compliance to clopidogrel was 99% at 6 months in both our groups, and 97% at 12 months in the longer DAPT group. On the contrary, data from real life registries have reported a P2Y₁₂ inhibitor discontinuation by 30 days of 13%[16]. Granted, one could argue that both the lower pre-test likelihood for ST as well as the good compliance to DAPT might have permitted a safer discontinuation of P2Y₁₂ receptor antagonist after 6-month without increasing the rate of adverse event. To this regard, only the premature DAPT discontinuation due to non-compliance or bleeding (disruption) has been shown to be associated with increased risk of adverse events [14, 17].

Related to the impact of DES type on outcome of DM patients, it has been shown that after second-generation DES implantation the event rates of diabetic patients remains considerably higher compared to the general population, especially in the subset of insulin-treated DM patients[18, 19]. Consistently, we found that the insulin-treated diabetic patients had a worse outcome compared to non insulin-requiring, irrespective of the DES type or DAPT duration. Similarly, Park et al [20] found a comparable result between the Xience everolimus-eluting stent and the Resolute zotarolimus-eluting stent in 1,855 all-comer diabetic patients with a final low incidence of TLF (3.5%) and ST (0.3%) at 1 year, suggesting excellent safety of both stent types. Notwithstanding, the patient-related events were 3-fold higher than stent-related events, highlighting the importance

of integrated secondary prevention and medical management of comorbidities in diabetes, especially when insulin-treated, during follow-up. Related to the adverse prognostic impact of female gender, our results are consistent with those of previous reports mainly focused on the impact of gender on outcome [21]. These findings seem to be associated with the prevalence of risk factors and the smaller vessels' diameter observed in women [22, 23].

LIMITATIONS

Patients included in our study were at low risk, with lower extent and complexity of CAD when compared to the diabetic subgroups of other clinical trials or registry. Therefore, our results cannot be extended to higher risk or to ACS patients, for which the indication for prolonged (≥ 12 months) DAPT is endorsed by ESC and ACC/AHA guidelines[1, 24].

Secondly, our results may be very well due to type II error and thus considered exploratory, notwithstanding the absolute difference of the composite primary end-point was as low as 1.5% and may be considered reassuring on clinical ground. We did not include patients under newer antithrombotic agents as an alternative to clopidogrel, such as ticagrelor and prasugrel, which have been shown to offer a more favorable outcome compared to clopidogrel particularly in DM patients[25, 26]. Notwithstanding, to date clopidogrel remains the approved P2Y₁₂ receptor antagonist in the setting of stable CAD[1].

To note, in the 6-month DAPT group, 28% of patients received clopidogrel at 12 months. It's therefore possible that patients with high-risk thrombotic profile might have received DAPT longer than 6 months even if they were assigned to the 6-month DAPT group. Notwithstanding, the per-protocol analysis excluding 61 patients with 3 primary events confirms the results of the intention-to-treat analysis.

It will be interesting also to see outcomes after longer follow-up, because some of the patient-related (thus not only stent-related) events might be expected beyond 2-year after PCI.

CONCLUSIONS

In DM patients treated by second-generation DES PCI, a DAPT regimen prolonged beyond 6-month did not seem to have any additional benefit in the prevention of ischemic or bleeding events. Insulin-requiring status was the major predictor of adverse outcome during follow-up, irrespective of DAPT duration.

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FIGURE LEGEND

FIGURE 1. CONSORT Flow Diagram Showing the Study Design of the SECURITY trial - diabetes substudy.

FIGURE 2. Kaplan-Meier Estimates of the Probability of Occurrence of the Primary Endpoint at 12 months.

FIGURE 3. Kaplan-Meier Estimates of the Probability of Occurrence of the Secondary Endpoint at 24 months.

FIGURE 4. Subgroup analyses for the Occurrence of the Primary Endpoint at 12 Months (a) and of the Secondary Endpoint at 24 Months (b).

FIGURE 5. Kaplan-Meier Estimates of the Probability of occurrence of the Primary (a) and Secondary (b) Endpoints according to DAPT duration and Insulin-requiring status

6-M = 6-month; 12-M = 12-month; CONSORT = Consolidated Standards of Reporting Trials; DAPT = dual antiplatelet therapy; FU = follow-up; ITT = intention-to-treat; SECURITY = Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month DAPT.

Fig. 1

Fig. 2

Fig. 3

a)

DAPT = dual antiplatelet therapy; NIDDM = non insulin-dependent diabetes mellitus; IDDM = insulin-dependent diabetes mellitus;
PCI = percutaneous coronary intervention

Fig. 4a

b)

DAPT = dual antiplatelet therapy; NIDDM = non insulin-dependent diabetes mellitus; IDDM = insulin-dependent diabetes mellitus;
PCI = percutaneous coronary intervention

Fig. 4b

a)

Fig. 5a

Fig. 5b

TABLE 1. Baseline Clinical Characteristics of Diabetic Patients Receiving 6- and 12-Month DAPT.
Values are mean $\pm$ SD or n (%).

	6-Month DAPT (n = 206)	12-Month DAPT (n = 223)	P value
Age, yrs	65.5 $\pm$ 10.1	66.7 $\pm$ 9.1	0.21
Female	58 (28.2)	58 (26.0)	0.70
Diabetes mellitus			
NID	162 (78.6)	179 (80.3)	0.77
ID	44 (21.4)	44 (19.7)	
Hypertension	170 (82.5)	179 (80.3)	0.63
Dyslipidemia	143 (69.4)	158 (70.9)	0.83
Smoker status			
Never smoked	88 (42.7)	80 (35.9)	0.49
Previous smoker	69 (33.5)	80 (35.9)	
Active smoker	39 (18.9)	45 (20.2)	
Previous MI			
NSTEMI > 48h	23 (11.2)	18 (8.1)	0.35
STEMI > 48h	26 (12.6)	20 (9.0)	0.29
Previous PCI	47 (22.8)	38 (17.0)	0.17
Previous CABG	12 (5.8)	16 (7.2)	0.71
LVEF, %	55.8 $\pm$ 9.7	55.7 $\pm$ 9.1	0.97
Clinical presentation			
Stable angina	132 (64.1)	151 (67.7)	0.49
Unstable angina	74 (35.9)	72 (32.3)	
Baseline medications			
Aspirin	195 (94.7)	190 (85.2)	0.002
Clopidogrel	99 (48.1)	87 (39.0)	0.07
Statin	156 (75.7)	169 (75.8)	1.00
Heparin	119 (57.8)	125 (56.1)	0.79
Glycoprotein IIb/IIIa inhibitors	9 (4.4)	8 (3.6)	0.87

CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; IDDM = insulin-dependent diabetes mellitus;
LVEF = left ventricular ejection fraction; MI = myocardial infarction; NIDDM = non-insulin-dependent diabetes mellitus;
NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention;
STEMI = ST-segment elevation myocardial infarction.

TABLE 2. Baseline Lesion Characteristics of Diabetic Patients Receiving 6 vs. 12-Month DAPT.
Values are mean $\pm$ SD or n (%).

	6-Month DAPT (n = 206)	12-Month DAPT (n = 223)	P value
Number of lesions			
1-vessel disease	94 (45.6)	116 (52.0)	0.26
2-vessel disease	87 (42.2)	77 (34.5)	
3-vessel disease	25 (12.1)	30 (13.5)	
Main branch lesion distribution			
Left anterior descending artery	114 (39.0)	128 (41.0)	0.16
Left circumflex artery	56 (19.0)	55 (18.0)	
Diagonal artery	25 (8.0)	20 (6.0)	
OM and RI arteries	26 (9.0)	46 (15.0)	
Right coronary artery	95 (32.0)	88 (28.0)	
Bifurcation	22 (10.7)	27 (12.1)	0.75
Baseline TIMI flow grade <3	36 (17.5)	40 (17.9)	1.00
AHA/ACC classification			
Class B	207 (70.2)	209 (67.4)	0.35
Class C	57 (19.3)	71 (22.9)	
Baseline visual estimate			
Lesion length, mm	17.1 $\pm$ 8.7	19.1 $\pm$ 13.3	0.15
Reference vessel diameter, mm	2.8 $\pm$ 0.5	2.9 $\pm$ 0.4	0.12
Minimal lumen diameter, mm	0.6 $\pm$ 0.5	0.6 $\pm$ 0.6	0.44
Diameter stenosis	83.5 $\pm$ 10.1	83.9 $\pm$ 9.9	0.67

ACC = American College of Cardiology; AHA = American Heart Association; DAPT = dual antiplatelet therapy;
OM = obtuse marginal; RI = ramus intermedius; TIMI = Thrombolysis In Myocardial Infarction.

TABLE 3. - Procedural and In-Hospital Outcomes of Diabetic Patients Receiving 6 vs. 12-Month DAPT.
Values are mean $\pm$ SD or n (%).

	6-Month DAPT (n = 206)	12-Month DAPT (n = 223)	P value
Femoral access	58 (28.2)	63 (28.3)	1.00
Radial access	146 (70.9)	159 (71.3)	1.00
Total number of treated vessels	257	267	
Total number of treated lesions	292	309	
Treated lesions			
1 lesion	141 (68.0)	155 (70.0)	0.60
>1 lesion	65 (32.0)	68 (30.0)	
Average of treated lesions per patient	1.42 $\pm$ 0.7	1.39 $\pm$ 0.7	0.74
Total number of implanted stents	321	364	
Stents implanted			
Per patient	1.56 $\pm$ 0.9	1.63 $\pm$ 1.1	0.63
Per lesion	1.09 $\pm$ 0.5	1.17 $\pm$ 0.6	0.04
Balloon pre-dilation (main branch)	171 (58.6)	186 (60.2)	0.75
Stent deployment pressure (main branch), atm	14.7 $\pm$ 3.1	15 $\pm$ 2.7	0.08
Balloon post-dilation (main branch)	130 (44.5)	118 (38.2)	0.13
IVUS-guided stent implantation	7 (2.4)	10 (3.2)	0.70
Mean stent length (main branch), mm	19.2 $\pm$ 7.4	19.3 $\pm$ 7.1	0.68
Mean stent size (main branch), mm	2.9 $\pm$ 0.9	2.9 $\pm$ 0.4	0.46
Total implanted drug-eluting stent type			
Endeavor Resolute stent	146 (43.2)	148 (38.9)	0.28
Nobori stent	85 (25.1)	102 (26.8)	0.66
Biomatrix stent	21 (6.2)	26 (6.8)	0.85
Promus stent	34 (10.1)	56 (14.7)	0.07
Xience stent	30 (8.9)	26 (6.8)	0.38
Balloon only	17 (5.0)	16 (4.2)	0.73
Total implanted bare-metal stents	5 (1.5)	6 (1.6)	1.00
Single stent success	269 (97.8)	295 (99.3)	0.16
Stents in overlap	28 (9.6)	42 (13.6)	0.16
Final % stenosis = 0	257 (85.7)	278 (88.0)	0.47
Serious adverse events during hospitalization	3 (1.4)	0 (0.0)	0.11
Therapy at discharge			
Aspirin	205 (99.5)	221 (99.1)	1.00
Clopidogrel	204 (99.0)	220 (98.7)	1.00
Prasugrel	1 (0.5)	0 (0.0)	0.48
Ticagrelor	0 (0.0)	0 (0.0)	1.00

TABLE 4. Clinical Outcomes in Diabetic Patients Receiving 6 vs. 12-Month DAPT (%).

Outcome	6-Month DAPT (n = 206)	12-Month DAPT (n = 223)	Difference (90% CI)	P value
Primary endpoint				
Primary efficacy composite endpoint				
6-12 months	1 (0.5)	1 (0.4)	0.1 (-1.5 to 1.7)	0.86
12 months	8 (3.9)	12 (5.4)	-1.5 (-5.0 to 2.0)	0.83
Secondary endpoint				
Secondary efficacy composite endpoint				
12 months	9 (4.4)	14 (6.3)	-1.9 (-5.6 to 1.8)	0.91
12-24 months	3 (1.5)	5 (2.2)	-0.7 (-3.2 to 1.6)	0.62
All cause mortality				
30 days	0 (0.0)	0 (0.0)	-	-
30 days – 6 months	1 (0.5)	1 (0.4)	0.1 (-1.5 to 1.7)	0.89
6-12 months	0 (0.0)	0 (0.0)	-	-
12-24 months	1 (0.5)	2 (0.9)	-0.4 (-2.2 to 1.4)	0.27
Cardiac mortality				
30 days	1 (0.5)	0 (0.0)	0.5 (-0.8 to 2.1)	0.25
30 days – 6 months	0 (0.0)	1 (0.4)	-0.4 (-2.0 to 0.9)	0.32
6-12 months	0 (0.0)	0 (0.0)	-	-
12 months	1 (0.5)	1 (0.4)	0.1 (-1.5 to 1.7)	0.82
12-24 months	0 (0.0)	1 (0.4)	-0.4 (-2.0 to 0.9)	0.41
24 months	1 (0.5)	2 (0.9)	-0.4 (-2.2 to 1.4)	0.73
Myocardial infarction				
30 days	0 (0.0)	5 (2.2)	-2.2 (-4.5 to -0.5)	0.07
30 days – 6 months	2 (1.0)	1 (0.4)	0.6 (-1.1 to 2.5)	0.44
6-12 months	2 (1.0)	1 (0.4)	0.6 (-1.1 to 2.5)	0.38
12 months	4 (1.9)	7 (3.1)	-1.2 (-4.0 to 1.5)	0.75
12-24 months	2 (1.0)	0 (0.0)	1 (-0.4 to 2.9)	0.14
24 months	6 (2.9)	7 (3.1)	-0.2 (-3.1 to 2.8)	0.99
Definite or probable stent thrombosis				
30 days	1 (0.5)	0 (0.0)	0.5 (-0.8 to 2.1)	0.23
30 days – 6 months	0 (0.0)	1 (0.4)	-0.4 (-2.0 to 0.9)	0.36
6-12 months	0 (0.0)	0 (0.0)	-	-
12 months	1 (0.5)	1 (0.4)	0.1 (-1.5 to 1.7)	0.80
12-24 months	1 (0.5)	0 (0.0)	0.5 (-0.8 to 2.1)	0.29
24 months	2 (1.0)	1 (0.4)	0.6 (-1.1 to 2.5)	0.45
Urgent TVR (PCI or CABG)				
30 days	0 (0.0)	0 (0.0)	-	-
30 days – 6 months	1 (0.5)	0 (0.0)	0.5 (-0.8 to 2.1)	0.27
6-12 months	0 (0.0)	1 (0.4)	-0.4 (-2.0 to 0.9)	0.62
12 months	1 (0.5)	1 (0.4)	0.1 (-1.5 to 1.7)	0.74
12-24 months	0 (0.0)	1 (0.4)	-0.4 (-2.0 to 0.9)	0.40
24 months	1 (0.5)	2 (0.9)	-0.4 (-2.2 to 1.4)	0.73
Stroke				
30 days	0 (0.0)	0 (0.0)	-	-
30 days – 6 months	1 (0.5)	1 (0.4)	0.1 (-1.5 to 1.7)	0.81
6-12 months	0 (0.0)	0 (0.0)	-	-
12 months	1 (0.5)	1 (0.4)	0.1 (-1.5 to 1.7)	0.92
12-24 months	0 (0.0)	1 (0.4)	-0.4 (-2.5 to 1.4)	0.37
24 months	1 (0.5)	2 (0.9)	-0.4 (-2.2 to 1.4)	0.57
Type 3 or 5 BARC bleeding				
30 days	1 (0.5)	1 (0.4)	0.1 (-1.5 to 1.7)	0.24
30 days – 6 months	1 (0.5)	3 (1.3)	-0.8 (-2.9 to 1.0)	0.54

6-12 months	0 (0.0)	0 (0.0)	-	-
12 months	2 (1.0)	4 (1.8)	-0.8 (-3.1 to 1.3)	0.77
12-24 months	1 (0.5)	0 (0.0)	0.5 (-0.8 to 2.1)	0.27
24 months	3 (1.5)	4 (1.8)	-0.3 (-2.7 to 2.0)	0.49

Values are n (%). Event rates based on Kaplan-Meier estimates. The p values were calculated by log-rank test.

The confidence interval for differences in event rates has not been calculated in case of no clinical events in either group

BARC = Bleeding Academic Research Consortium; CI = confidence interval; TVR = target vessel revascularization; other abbreviations as in Table 1.