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Impact of diabetes on the outcomes in patients undergoing contemporary percutaneous coronary intervention: Analysis from the GLOBAL LEADERS study

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Abstract (250 words)

Background

Diabetes has been well recognized as a strong predictor for adverse outcomes after percutaneous coronary intervention (PCI), however, studies in the era of drug-eluting stent and potent P2Y12 inhibitors have shown conflicting results. We assessed ischemic and bleeding outcomes after contemporary PCI according to diabetic status.

Methods and results

We studied 15,957 patients in the GLOBAL LEADERS study with known baseline diabetic status. The primary endpoint was all-cause death or new Q-wave myocardial infarction at 2 years. The secondary safety endpoint was major bleeding defined as bleeding academic research consortium (BARC) type 3 or 5.

Out of 15957 patients with known diabetic status before PCI, 4,038 patients (25.1%) were diabetes. Patients with diabetes had significantly higher risk of primary endpoint at 2 years than non-diabetes (adjusted hazard ratio [HR] 1.36; 95% confidence interval [CI] 1.14-1.61). The difference was driven by a significantly higher risk of all-cause mortality at 2 years in diabetes than non-diabetes (adjusted HR 1.44, 95% CI 1.18-1.75). The risk of BARC 3 or 5 bleeding was not different between the two groups (adjusted HR 1.18, 95% CI 0.92-1.50). The effect of antiplatelet strategy (experimental versus reference strategy) on the primary endpoint and secondary safety endpoint at 2 years were not different between diabetes and non-diabetes.

Conclusions

Diabetic patients had higher risk of ischemic events after PCI than non-diabetic patients. The bleeding risk was not different between diabetes and non-diabetes. The outcomes of diabetic patients following PCI was not affected by the two different antiplatelet strategies.

Introduction

Diabetes mellitus is a chronic disease associated with a high morbidity and mortality. It is also a well-known risk factor for coronary artery disease (CAD).[1] Unsurprisingly, CAD is a major cause of death in diabetic patients. Incidence of diabetes has increased worldwide[2] and its prevalence in CAD patients undergoing percutaneous coronary intervention (PCI) has been reported to be as high as 20-30%.[3-5]

Diabetes has been well recognized as a strong predictor for adverse outcomes after PCI. In large pooled randomized trials, diabetes with or without insulin treatment was identified as independent predictor of major adverse cardiac events, cardiac death, and myocardial infarction (MI) after PCI trials[6]. However, recent studies have shown no difference in the risk of MI[5,7] and cardiac death[5] between diabetic and non-diabetic patients. It could be hypothesized that treatment with potent antiplatelet therapy together with the improvement in PCI practice may mitigate the negative impact of diabetes on adverse ischemic events[8].

The evidence on the risk of bleeding in diabetic patients treated with antiplatelet therapy was less well studied than the risk of ischemic event. In the Platelet Inhibition and Patient Outcomes (PLATO) study, diabetic patients presenting with acute coronary syndrome were associated with higher bleeding risk than non-diabetic patients regardless of the choice of P2Y12 receptor inhibitor (clopidogrel or ticagrelor)[9]. However, the studies in the setting of PCI has shown that diabetes was not associated with an increased risk of bleeding during dual antiplatelet therapy (DAPT)[10]. Furthermore, novel risk scores to predict bleeding after PCI did not identify the predictive value of diabetes[11,12]. In the GLOBAL LEADERS study, when compared with conventional DAPT, long-term ticagrelor monotherapy tended to lower the risk of all-cause mortality or new Q wave MI after PCI with similar risk of bleeding at 2

years[13]. The effect of antiplatelet strategy on the ischemic and bleeding outcomes may differ between diabetic and non-diabetic patients undergoing PCI.

Therefore, we aimed to compare the ischemic and bleeding outcomes after contemporary PCI in patients with or without diabetes. In addition, the impact of diabetes on the effect of two antiplatelet strategies in the GLOBAL LEADERS study was also assessed.

Methodology

Study design and population

The GLOBAL LEADERS study was an investigator-initiated, randomized, multi-center, open-label trial comparing two strategies of antiplatelet therapy after PCI using uniformly bivalirudin and biolimus A9 eluting stents (Biomatrix) in all-comers patients[13]. In the experimental strategy, patients received aspirin 75-100 mg once daily in combination with ticagrelor 90 mg twice daily for one month; followed by ticagrelor 90 mg twice daily alone for 23 months (irrespective of the clinical presentation). In the reference strategy, patients received aspirin 75-100 mg daily in combination with either clopidogrel 75 mg once daily in patients with stable CAD or ticagrelor 90 mg twice daily in patients with acute coronary syndrome (ACS) for 1 year; followed by aspirin 75-100 mg once daily alone for the following 12 months (from 12 to 24 months after PCI).

The main study enrolled 15,991 patients between July 2013 to November 2015 in an "all-comers" design[13]: no restriction regarding clinical presentation, complexity of the lesions or number of stents used. Since 23 patients withdrew consent and requested data deletion from the database, a total of 15,968 patients remained in the study. Patients were followed up at 30 days and 3, 6, 12, 18 and 24 months after the index PCI. Electrocardiogram (ECG) was obtained at discharge, 3-month and 2-year follow up and during the follow up if there was suspected ischemic events or repeat revascularization. All ECGs were analyzed at the core

laboratory (Cardialysis, Rotterdam, Netherlands) by technicians who were blinded to the treatment assignments.

Patients with diabetes mellitus was a pre-specified subgroup of the GLOBAL LEADERS study. In the present study, patients were stratified according to status of diabetes mellitus before PCI. Patients with diabetes mellitus were also stratified into non-insulin treated diabetes or insulin-treated diabetes. Patients were classified as insulin-treated diabetes if they received any kind of insulin therapy, and non-insulin treated diabetes if they were treated with oral hypoglycemic drug or lifestyle modification. The analysis was based on the intention-to-treat population. The GLOBAL LEADERS study was approved by the institutional review board at each participating institution. All patients provided informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practices. An independent data and safety monitoring committee oversaw the safety of all patients.

Objectives and endpoints

The present study aimed to assess the risk of diabetic patients with CAD undergoing contemporary PCI treatment and to evaluate interaction between diabetes and antiplatelet strategies on the outcomes after PCI.

The primary ischemic endpoint was all-cause death or new Q wave MI at 2 years. The secondary safety endpoint was major bleeding defined as bleeding academic research consortium (BARC) type 3 or 5[14]. The additional secondary endpoints were cardiac death, patient-oriented composite endpoint (POCE) and net adverse clinical endpoint (NACE). POCE was defined as composite endpoint of all-cause death, any stroke, any MI and any revascularization[15]. NACE included POCE plus BARC 3 or 5 bleeding. Time to first event analysis was used for the analysis of composite endpoint. Individual components of POCE

and NACE, definite or probable stent thrombosis according to academic research consortium were reported[16].

Statistical analysis

Continuous variables are presented as mean ± standard deviation and were compared using independent t test. Categorical variables are presented as counts and percentage and were compared using Chi square test. Cumulative rates of events were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariable Cox regression was used to determine if diabetes was an independent predictor for the outcomes at 2 years. The covariables included in the model were age, sex, body mass index (BMI), peripheral vascular disease (PVD), prior MI, chronic obstructive pulmonary disease (COPD), renal impairment (defined as estimate glomerular filtration rate < 60 ml/min using the Modification of Diet in Renal Disease equation[17]) and acute coronary syndrome as a clinical presentation. Interaction analysis between diabetes and antiplatelet strategy on the outcomes was assessed in the Cox regression model including main effect (diabetes and antiplatelet strategy) and interaction terms. Analyses were performed in R version 3.4.2 (R foundation, Vienna, Austria). All p values were two-sided and the statistical significance was considered if the value was less than 0.05.

Results

Of 15957 patients with known diabetic status before PCI, 4,038 patients (25.1%) were diabetes. Of 4002 diabetic patients with known insulin treatment status, 2779 patients were non-insulin treated diabetes and 1223 patients were insulin-treated diabetes. Compared with non-diabetes, diabetic patients were older, had higher mean BMI and higher prevalence of comorbidities such as hypertension, hypercholesterolemia, PVD, COPD, impaired renal

function, previous stroke, history of previous PCI or coronary artery bypass grafting (CABG) and previous MI (table 1). Non-diabetic patients were more likely to be current smoker and to present with MI than diabetic patients. There was no difference in the number of lesions treated, percentage of multivessel PCI and mean stent length between diabetes and non-diabetes. Compared with non-diabetes, the average number of stent was higher whereas the average stent diameter and the percentage of bifurcation PCI were lower in diabetes.

Compared with non-insulin treated diabetes, patients with insulin-treated diabetes had higher mean BMI and higher prevalence of PVD, impaired renal function, previous stroke, previous MI, previous PCI and previous CABG and were more likely to present with stable CAD. The mean stent diameter in insulin-treated diabetes was lower than non-insulin treated diabetes.

Two-year outcomes between diabetes and non-diabetes

The outcomes at 2 years are shown in figure 1. Patients with diabetes had significantly higher risk of primary endpoint at 2 years than non-diabetes (adjusted hazard ratio [HR] 1.36; 95% confidence interval [CI] 1.14-1.61). The difference was driven by the significantly higher risk of all-cause mortality at 2 years in diabetes than non-diabetes (adjusted HR 1.44, 95% CI 1.18-1.75). The two-year risk of ischemic stroke, any MI, any revascularization, POCE, and NACE was significantly higher in diabetes than non-diabetes (figure 1). The risk of stent thrombosis and the risk of bleeding either BARC 2,3 or 5 bleeding or BARC 3 or 5 bleeding was not different between the two groups.

Insulin-treated versus non-insulin treated diabetes

Two-year outcomes between insulin-treated diabetes, non-insulin treated diabetes and non-diabetes are presented in table 2. Compared with non-diabetes, insulin-treated diabetes

had significantly higher risk of primary endpoint at 2 years (adjusted HR 1.75; 95% CI 1.38-2.23). The difference was driven by the significantly higher risk of all-cause mortality at 2 years in the insulin-treated diabetes than the non-diabetes (adjusted HR 1.93, 95% CI 1.47-2.53). The risk of primary endpoint and all-cause mortality were not different between non-insulin treated diabetes and non-diabetes (primary endpoint; adjusted HR 1.18, 95% CI 0.96-1.45, all-cause mortality; adjusted HR 1.22, 95% CI 0.96-1.54). Compared with non-diabetic, the adjusted hazard ratio for POCE at 2 years was 1.28 (95% CI 1.15-1.43) to 1.54 (95% CI 1.34-1.77) in non-insulin treated diabetes and insulin-treated diabetes respectively. Similar increases in the hazard ratio for NACE, ischemic stroke, any MI and any revascularization were observed in non-insulin treated and insulin-treated diabetes when compared with non-diabetes. The risk of definite, definite or probable stent thrombosis, and BARC 3 or 5 bleeding were not different among the three groups.

Impact of diabetic status and allocated antiplatelet strategies on outcomes after PCI

The effect of antiplatelet strategy (experimental versus reference strategy) on the primary endpoint and other outcomes at 2 years were not different between diabetes and non-diabetes (figure 2). The results were not changed when the interaction analysis was performed according to the stratification by the insulin treatment status (supplementary figure 2).

Discussion

We studied the outcomes and the effect of different antiplatelet strategies in diabetic patients stratified by the status of insulin treatment in the large all-comers population undergoing contemporary PCI worldwide. The salient findings from the present study are 1) patients with diabetes either treated with insulin or not had significantly higher risk of

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ischemic event after contemporary PCI treatment. 2) The risk of stent thrombosis was similar among the three groups. 3) Bleeding risk after PCI were not different among non-diabetes, non-insulin treated and insulin-treated diabetes. 4). The outcomes of diabetic patients following PCI was not affected by the two different antiplatelet strategies.

Ischemic risk after PCI in diabetes

Drug-eluting stents improved the outcomes in patients with CAD undergoing PCI when compared with bare-metal stent[18]. In addition, the newer-generation DES with biocompatible polymer has shown to reduce the risk of composite ischemic endpoint and stent thrombosis when compared with the first-generation DES[19,20]. Treatment with potent P2Y12 receptor inhibitor in ACS patients undergoing PCI improved survival and lowered the composite ischemic endpoint when compared with clopidogrel[9].

The current PCI practice using newer-generation DES, potent P2Y12 inhibitors in ACS patients and guideline-directed optimal therapy has improved the outcomes of patients undergoing PCI[21]. The improvement has been demonstrated in both diabetic and non-diabetic patients[9]. In the pooled analysis of 6081 patients treated with new-generation DES by Koskinas et al, although the diabetic patients experienced higher risk of repeat target lesion revascularization than non-diabetic patients, the risk of cardiac death, MI and stent thrombosis were not different between the two groups[5]. In the analysis from the BIONICS randomized trial, the rate of target lesion failure at 1 year in diabetes was higher than non-diabetes while the rate of cardiac death, MI and stent thrombosis did not differ between the two groups[7]. In a registry of 4812 consecutive patients treated with second-generation DES, the risk of patient-oriented composite outcome in non-insulin treated diabetes was higher than non-diabetes (adjusted HR 1.21, 95% CI 1.00-1.47, p value 0.049), however, the lower end of confidence interval and p value were close to the level of no difference[4]. The risk of

all-cause death, cardiac death, and stent thrombosis were similar between non-diabetes and non-insulin treated diabetes while the risk of these events and patient-oriented composite outcomes were significantly higher in insulin-treated diabetes when compared with the two groups[4]. Recently, in patients with three-vessel disease treated with state-of-the-art PCI, the rate of major adverse cardiac and cerebrovascular events at 2 years was not different between diabetes and non-diabetes (15.0% vs. 12.5%, p = 0.50)[22].

In the present study, although the risk of primary efficacy endpoint and its components were not different between non-diabetes and non-insulin treated diabetes, the risk of POCE, ischemic stroke, any MI, and any revascularization were significantly higher in non-insulin treated diabetes than non-diabetes. The risk of these events was even higher in insulin-treated diabetes when compared with non-diabetes. To date, the present study is the largest cohort of all-comers patients that received contemporary PCI treatment. Although the randomization was not stratified by diabetic status and sample size calculation was not based on the information in diabetes, the large number of diabetic patients in the GLOBAL LEADERS study improved the precision and the power of the analysis. This fact could be an explanation why the risk difference in some outcomes were not demonstrated in the previous studies. Our study is unique in the sense that the PCI in the GLOBAL LEADERS study was standardized since 87.3% of patients received bivalirudin-assisted PCI and almost 95% of lesion were treated with biolimus-A9 eluting stent[13]. Furthermore, ACS patients were treated with potent P2Y12 inhibitor (ticagrelor). The confounding effect of different type of stent and periprocedural antithrombotic medication seen in previous studies were eliminated from the present analysis. Hence, our results emphasize that diabetic patients regardless of the status of the insulin treatment were still experiencing higher risk of major ischemic events after contemporary PCI and the intensive care to reduce the risk in this high-risk subgroup is mandatory.

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Intriguingly, the risk of stent thrombosis either definite or probable stent thrombosis was not different among the three groups. Diabetes has been long recognized as a well-known predictor for stent thrombosis[23,24]. The risk of stent thrombosis in diabetic patients treated with first-generation DES were 3.71 time higher than non-diabetes[25] whereas the hazard ratio of diabetes versus non-diabetes for definite stent thrombosis was lower (HR 1.79, 95% 0.99-3.24) in the era of second-generation DES[6]. Although it could be argued that our analysis may be underpowered to detect the difference in the risk of stent thrombosis, the similar risk of definite stent thrombosis among diabetes and non-diabetes in the present study is in line with the other recently published data[7,26].

Bleeding risk after PCI in diabetes

Platelets of diabetic patients are more reactive in adhesion, activation, degranulation and aggregation than the platelets of healthy controls[27]. The turnover rate and the number of reticulated platelets in diabetic patients were also higher which resulted in the increased endothelial cell adhesion[28]. Moreover, platelets of diabetic patients were more resistant to antiplatelet agent[29,30]. From these evidences, it could be hypothesized that the bleeding risk of diabetic patients treated with antiplatelet would be at least similar or even lower than non-diabetic patients.

Recent studies have shown that diabetes was not an independent predictor for bleeding after PCI in the era of DES. A large individual patient data meta-analysis of 11,473 patients studying the outcomes between short-term or long-term DAPT after DES implantation according to the diabetic status showed similar bleeding risk between diabetic and non-diabetic patients[26]. Diabetic patients even experienced lower bleeding risk than non-diabetic patients after PCI in a multicenter US registry of consecutive PCI patients[31]. Nonetheless, most of the patients in these studies received clopidogrel as a P2Y12 inhibitor.

The present study assessed the risk of bleeding according to diabetic status in patients undergoing contemporary PCI treatment in which majorities of the patients received potent P2Y12 inhibitor. Our findings were similar to the results from the previous studies of diabetic patients treated with DAPT after PCI in which the risk of bleeding at 2 years was not different among diabetes and non-diabetes.

Impact of antiplatelet strategies on PCI results in diabetes

Considering that diabetic patients are at higher risk of ischemic event and similar bleeding risk to the non-diabetic patients undergoing PCI, diabetic-specific antiplatelet regimens may be needed[32]. The more aggressive and potent antiplatelet regimens in diabetic patients might theoretically reduce the ischemic risk without increasing the risk of bleeding[8]. However, our results did not support the above hypothesis since no significant interaction between diabetic status and antiplatelet strategies on any outcomes was observed.

The complexity of CAD could affect the outcomes of diabetic patients treated with PCI. The pooled analysis of randomized trials in 18441 patients has shown that the risk of repeat revascularization in diabetic patients was dependent on the coronary lesion complexity as defined by American College of Cardiology and American Heart Association classification[6]. Hence, the outcomes and selection of the optimal platelet strategy may not solely depend on the diabetic status but may also depend on complexity of CAD or other comorbidities. The ongoing TWILIGHT study (NCT 02270242) is comparing two antiplatelet strategies in high-risk patients after PCI. High-risk patient is defined as having at least one high-risk angiographic criteria and at least one high-risk clinical characteristics. Medically treated diabetes is one of the clinical criteria of high-risk patients. The THEMIS study (NCT 01991795) is testing the impact of ticagrelor in diabetic patients with stable CAD

without prior MI. Both studies may provide the information added to the literature on the optimal antiplatelet strategy after PCI in diabetic patients.

Limitations

First, our analyses are considered exploratory and statistical adjustment for multiple testing was not performed. Therefore, the results should be interpreted with caution and considered as hypothesis-generating.[33] Secondly, the randomization in the GLOBAL LEADERS study was not stratified by diabetic status. Hence, the results on the effect of antiplatelet strategy and diabetic status on the outcomes are at risk for a type II error. Finally, there was no adjudication for serious adverse events due to limited financial resources and the endpoints were site-reported with the exception of primary endpoint: all-cause death and new Q wave MIs assessed by an independent ECG core lab. Nevertheless, there was regular monitoring and on-site visits for consistency of event definitions and underreport of the events.

Conclusions

In this subgroup analysis of the GLOBAL LEADERS study, diabetic patients with or without insulin therapy still had higher risk of adverse ischemic events than non-diabetic patients. The outcomes of diabetic patients following PCI was not affected by the two different antiplatelet strategies.

Table and figure legends

Table 1: Clinical, angiographic and procedural characteristics of patients with or without diabetes mellitus

Table 2: Two-year outcomes among non-diabetes, non-insulin treated diabetes and insulin-treated diabetes

Figure 1: Two-year outcomes between patients with or without diabetes mellitus

Figure 2: Two-year outcomes in patients with or without diabetes mellitus according to antiplatelet strategy

Supplementary figure 1: two-year outcomes among non-diabetes, non-insulin treated and insulin-treated diabetes according to antiplatelet strategy

Table 1: Clinical, angiographic and procedural characteristics of patients with or without diabetes mellitus

Variable	Non-diabetes (N= 11919)	Diabetes (N=4038)	P value†	Non-insulin treated diabetes (N=2779)	Insulin-treated diabetes (N=1223)	P value‡
Mean age (years) ± SD	63.93±10.50	66.33±9.48	<0.0001	66.27±9.44	66.51±9.61	0.4647
Mean body-mass index (kg/m²) ± SD	27.69±4.33	29.66±5.01	<0.0001	29.45±4.85	30.13±5.34	0.0001
Hypertension	8211 (69.16)	3497 (86.69)	<0.0001	2397 (86.32)	1067 (87.39)	0.3862
Hypercholesterolemia	7699 (66.65)	3064 (78.38)	<0.0001	2112 (78.40)	933 (78.87)	0.7746
Current smoker	3364 (28.22)	800 (19.81)	<0.0001	565 (20.33)	229 (18.72)	0.2581
Peripheral vascular disease	604 (5.11)	401 (10.04)	<0.0001	254 (9.23)	141 (11.67)	0.0214
Chronic obstructive pulmonary disease	572 (4.82)	249 (6.20)	0.0007	159 (5.75)	87 (7.18)	0.0986
Previous major bleeding	74 (0.62)	24 (0.60)	0.9480	17 (0.61)	7 (0.57)	1
Impaired renal function	1332 (11.25)	838 (20.81)	<0.0001	484 (17.47)	352 (28.83)	<0.0001
Previous stroke	257 (2.16)	164 (4.07)	<0.0001	92 (3.32)	70 (5.73)	0.0005
Previous MI	2623 (22.06)	1086 (27.00)	<0.0001	668 (24.11)	406 (33.39)	<0.0001
Previous PCI	3596 (30.20)	1623 (40.22)	<0.0001	1046 (37.67)	556 (45.50)	<0.0001
Previous CABG	570 (4.79)	373 (9.25)	<0.0001	232 (8.36)	139 (11.37)	0.0030
Clinical presentation			<0.0001			0.0485
Stable coronary artery disease	6041 (50.68)	2434 (60.28)		1647 (59.27)	772 (63.12)	
Unstable angina	1479 (12.41)	542 (13.42)		362 (13.03)	163 (13.33)	
Non-ST-elevation MI	2644 (22.18)	727 (18.00)		524 (18.86)	200 (16.35)	
ST-elevation MI	1755 (14.72)	335 (8.30)		246 (8.85)	88 (7.20)	
Number of lesion treated, mean ± SD	1.43 ± 0.74	1.46 ± 0.75	0.0503	1.45 ± 0.74	1.48 ± 0.77	0.1319
Lesions treated per patient			0.0513			0.0649
One lesion	8118 (68.62)	2665 (66.56)		1860 (67.49)	778 (64.19)	
Two lesions	2672 (22.59)	969 (24.20)		640 (23.22)	323 (26.65)	
Three or more lesions	1040 (8.79)	370 (9.24)		256 (9.29)	111 (9.16)	
Left main PCI	312 (2.64)	117 (2.92)	0.3666	79 (2.87)	38 (3.14)	0.7194
RCA PCI	4476 (37.84)	1474 (36.81)	0.2559	1041 (37.77)	419 (34.57)	0.0587
LAD PCI	6089 (51.47)	1961 (48.98)	0.0067	1350 (48.98)	599 (49.42)	0.8259
LCX PCI	3666 (30.99)	1340 (33.47)	0.0038	904 (32.80)	419 (34.57)	0.2925
Bypass graft PCI	118 (1.00)	100 (2.50)	<0.0001	66 (2.39)	34 (2.81)	0.5157
Stent number per patient, mean ± SD	1.71 ± 1.08	1.75 ± 1.09	0.0323	1.75 ± 1.10	1.76 ± 1.08	0.7433
Multivessel PCI	2645 (22.36)	930 (23.23)	0.2652	647 (23.48)	277 (22.85)	0.6997
Bifurcation PCI	1905 (16.10)	590 (14.74)	0.0425	416 (15.09)	169 (13.94)	0.3719
Stent length per patient (mm), mean±SD	24.88 ± 12.91	25.26 ± 13.70	0.1141	25.46 ± 13.87	24.82 ± 13.40	0.1871
Stent diameter per patient (mm), mean±SD	3.01 ± 0.43	2.96 ± 0.43	<0.0001	2.98 ± 0.43	2.92 ± 0.41	0.0001

Values shown are % (n) otherwise indicated
†comparison between diabetes and non-diabetes
‡comparison between non-insulin treated diabetes and insulin-treated diabetes

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2200patients may be not bad to look for the impact on outcome. Are patients with diabetes and real dysfunction doing worse than others. Is there an impact from the treatment strategy?

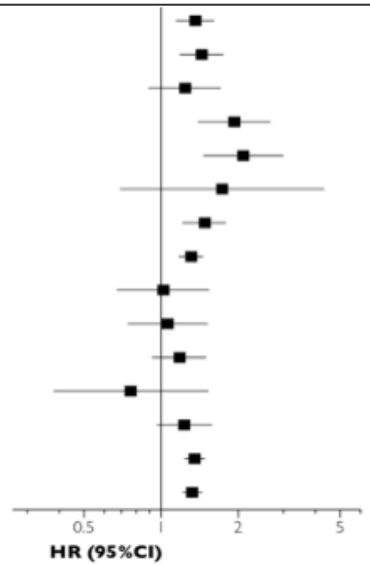
Table 2: Two-year outcomes among non-diabetes, non-insulin treated diabetes and insulin-treated diabetes

Outcomes at 2 years	Non-diabetes (N=11919)	Non-insulin treated diabetes (N=2779)	Insulin-treated diabetes (N=1223)	Unadjusted HR (95% CI)		Adjusted HR (95% CI)	
				Non-insulin treated diabetes/Non-diabetes	Insulin-treated diabetes/Non-diabetes	Non-insulin treated diabetes/Non-diabetes	Insulin-treated diabetes/Non-diabetes
All-cause death or new Q wave MI	424 (3.56)	132 (4.76)	94 (7.69)	1.34 (1.10-1.63)	2.20 (1.76-2.75)	1.18 (0.96-1.45)	1.75 (1.38-2.23)
All-cause death	302 (2.54)	97 (3.50)	75 (6.13)	1.38 (1.10-1.74)	2.46 (1.91-3.16)	1.22 (0.96-1.54)	1.93 (1.47-2.53)
New Q wave MI	127 (1.08)	38 (1.40)	21 (1.76)	1.29 (0.90-1.85)	1.64 (1.03-2.60)	1.16 (0.80-1.70)	1.44 (0.89-2.33)
Any Stroke	96 (0.82)	39 (1.44)	27 (2.27)	1.75 (1.21-2.54)	2.80 (1.83-4.29)	1.67 (1.15-2.45)	2.61 (1.67-4.09)
Ischemic stroke	75 (0.64)	32 (1.18)	24 (2.02)	1.84 (1.21-2.78)	3.18 (2.01-5.04)	1.75 (1.15-2.66)	3.03 (1.87-4.91)
Hemorrhagic stroke	14 (0.12)	5 (0.19)	3 (0.25)	1.53 (0.55-4.26)	2.12 (0.61-7.36)	1.68 (0.59-4.81)	1.88 (0.51-6.98)
Any MI	326 (2.79)	113 (4.15)	58 (4.89)	1.50 (1.21-1.85)	1.77 (1.34-2.34)	1.48 (1.19-1.84)	1.49 (1.11-2.01)
Any revascularization	1056 (9.05)	315 (11.58)	156 (13.18)	1.29 (1.14-1.47)	1.49 (1.26-1.76)	1.28 (1.12-1.46)	1.39 (1.17-1.66)
Definite stent thrombosis	95 (0.81)	24 (0.87)	8 (0.67)	1.09 (0.69-1.70)	0.83 (0.40-1.70)	1.10 (0.69-1.74)	0.77 (0.37-1.62)
Definite or probable stent thrombosis	119 (1.01)	34 (1.23)	10 (0.83)	1.23 (0.84-1.80)	0.83 (0.43-1.57)	1.18 (0.80-1.76)	0.74 (0.38-1.44)
BARC 3 or 5 bleeding	233 (1.99)	62 (2.27)	37 (3.11)	1.14 (0.86-1.51)	1.57 (1.11-2.22)	1.09 (0.82-1.44)	1.42 (0.99-2.03)
BARC 5 bleeding	35 (0.30)	6 (0.22)	5 (0.43)	0.74 (0.31-1.75)	1.41 (0.55-3.59)	0.64 (0.27-1.54)	1.03 (0.39-2.74)
BARC 3 bleeding	215 (1.84)	60 (2.20)	34 (2.85)	1.20 (0.90-1.60)	1.56 (1.09-2.24)	1.16 (0.86-1.55)	1.44 (0.99-2.09)
POCE	1472 (12.48)	452 (16.41)	250 (20.68)	1.34 (1.20-1.49)	1.73 (1.51-1.98)	1.28 (1.15-1.43)	1.54 (1.34-1.77)
NACE	1617 (13.71)	489 (17.75)	269 (22.23)	1.32 (1.19-1.46)	1.69 (1.49-1.93)	1.26 (1.13-1.39)	1.50 (1.31-1.72)

BARC: bleeding academic research consortium, CI: confidence interval, HR: hazard ratio, MI: myocardial infarction, NACE; net adverse clinical events, POCE; patient-oriented composite endpoints.

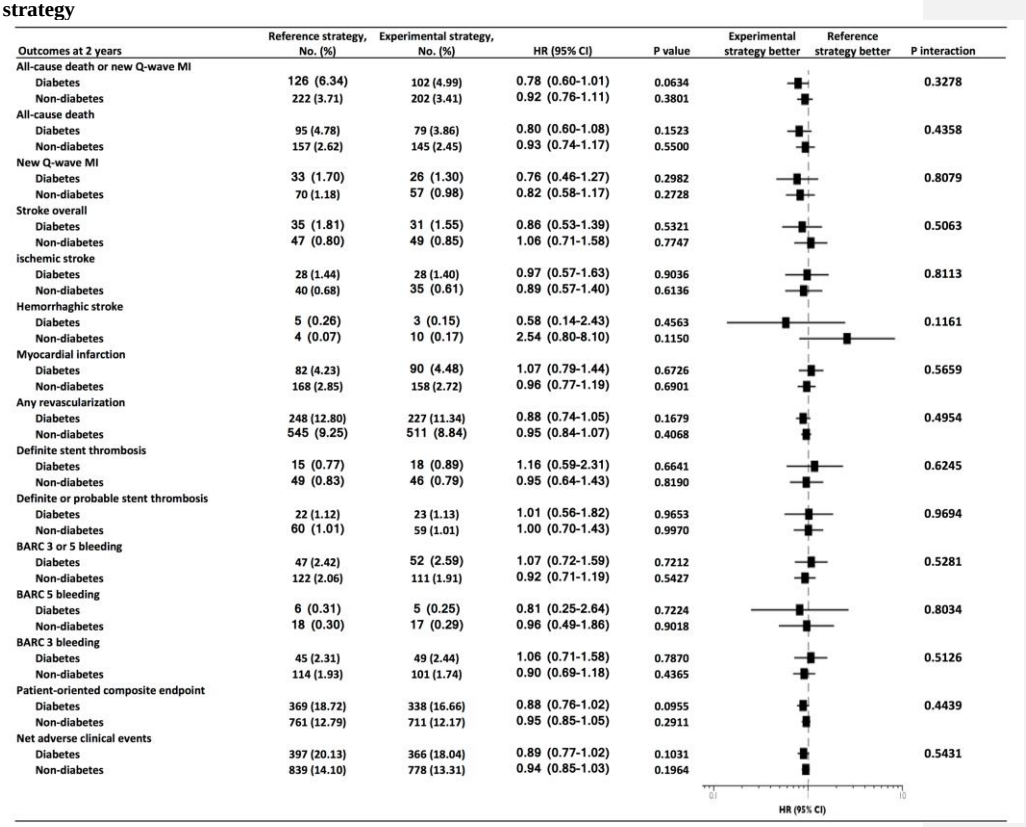
Figure 1: Two-year outcomes between patients with or without diabetes mellitus

Outcomes at 2 years	Non-diabetes (N=11919)	Diabetes (N=4038)	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All-cause death or new Q wave MI	424 (3.56)	228 (5.66)	1.60 (1.36-1.88)	< 0.0001	1.36 (1.14-1.61)	0.0004
All-cause death	302 (2.54)	174 (4.31)	1.71 (1.42-2.07)	< 0.0001	1.44 (1.18-1.75)	0.0003
New Q wave MI	127 (1.08)	59 (1.49)	1.38 (1.02-1.88)	0.0394	1.24 (0.89-1.71)	0.1990
Any Stroke	96 (0.82)	66 (1.67)	2.05 (1.50-2.80)	< 0.0001	1.93 (1.39-2.67)	0.0001
Ischemic stroke	75 (0.64)	56 (1.42)	2.22 (1.57-3.14)	< 0.0001	2.09 (1.46-3.00)	0.0001
Hemorrhagic stroke	14 (0.12)	8 (0.20)	1.69 (0.71-4.04)	0.2345	1.73 (0.69-4.33)	0.2382
Any MI	326 (2.79)	172 (4.36)	1.57 (1.31-1.89)	< 0.0001	1.48 (1.21-1.79)	0.0001
Any revascularization	1056 (9.05)	475 (12.06)	1.35 (1.21-1.50)	< 0.0001	1.31 (1.17-1.46)	< 0.0001
Definite stent thrombosis	95 (0.81)	33 (0.83)	1.03 (0.69-1.53)	0.8876	1.02 (0.67-1.54)	0.9311
Definite or probable stent thrombosis	119 (1.01)	45 (1.13)	1.12 (0.79-1.58)	0.5168	1.06 (0.74-1.52)	0.7563
BARC 3 or 5 bleeding	233 (1.99)	99 (2.51)	1.26 (1.00-1.59)	0.0540	1.18 (0.92-1.50)	0.1934
BARC 5 bleeding	35 (0.30)	11 (0.28)	0.93 (0.47-1.83)	0.8373	0.76 (0.38-1.53)	0.4465
BARC 3 bleeding	215 (1.84)	94 (2.38)	1.30 (1.02-1.65)	0.0356	1.23 (0.96-1.58)	0.1071
POCE	1472 (12.48)	707 (17.68)	1.45 (1.33-1.59)	< 0.0001	1.35 (1.23-1.48)	< 0.0001
NACE	1617 (13.71)	763 (19.07)	1.43 (1.31-1.55)	< 0.0001	1.32 (1.21-1.45)	< 0.0001



BARC: bleeding academic research consortium, CI: confidence interval, HR: hazard ratio, MI: myocardial infarction, NACE; net adverse clinical events, POCE; patient-oriented composite endpoints.

Figure 2: Two-year outcomes in patients with or without diabetes mellitus according to antiplatelet strategy



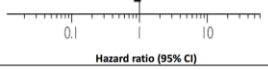
Outcomes at 2 years	Reference strategy, No. (%)	Experimental strategy, No. (%)	HR (95% CI)	P value	P interaction
All-cause death or new Q-wave MI					
Diabetes	126 (6.34)	102 (4.99)	0.78 (0.60-1.01)	0.0634	0.3278
Non-diabetes	222 (3.71)	202 (3.41)	0.92 (0.76-1.11)	0.3801	
All-cause death					
Diabetes	95 (4.78)	79 (3.86)	0.80 (0.60-1.08)	0.1523	0.4358
Non-diabetes	157 (2.62)	145 (2.45)	0.93 (0.74-1.17)	0.5500	
New Q-wave MI					
Diabetes	33 (1.70)	26 (1.30)	0.76 (0.46-1.27)	0.2982	0.8079
Non-diabetes	70 (1.18)	57 (0.98)	0.82 (0.58-1.17)	0.2728	
Stroke overall					
Diabetes	35 (1.81)	31 (1.55)	0.86 (0.53-1.39)	0.5321	0.5063
Non-diabetes	47 (0.80)	49 (0.85)	1.06 (0.71-1.58)	0.7747	
ischemic stroke					
Diabetes	28 (1.44)	28 (1.40)	0.97 (0.57-1.63)	0.9036	0.8113
Non-diabetes	40 (0.68)	35 (0.61)	0.89 (0.57-1.40)	0.6136	
Hemorrhaghic stroke					
Diabetes	5 (0.26)	3 (0.15)	0.58 (0.14-2.43)	0.4563	0.1161
Non-diabetes	4 (0.07)	10 (0.17)	2.54 (0.80-8.10)	0.1150	
Myocardial infarction					
Diabetes	82 (4.23)	90 (4.48)	1.07 (0.79-1.44)	0.6726	0.5659
Non-diabetes	168 (2.85)	158 (2.72)	0.96 (0.77-1.19)	0.6901	
Any revascularization					
Diabetes	248 (12.80)	227 (11.34)	0.88 (0.74-1.05)	0.1679	0.4954
Non-diabetes	545 (9.25)	511 (8.84)	0.95 (0.84-1.07)	0.4068	
Definite stent thrombosis					
Diabetes	15 (0.77)	18 (0.89)	1.16 (0.59-2.31)	0.6641	0.6245
Non-diabetes	49 (0.83)	46 (0.79)	0.95 (0.64-1.43)	0.8190	
Definite or probable stent thrombosis					
Diabetes	22 (1.12)	23 (1.13)	1.01 (0.56-1.82)	0.9653	0.9694
Non-diabetes	60 (1.01)	59 (1.01)	1.00 (0.70-1.43)	0.9970	
BARC 3 or 5 bleeding					
Diabetes	47 (2.42)	52 (2.59)	1.07 (0.72-1.59)	0.7212	0.5281
Non-diabetes	122 (2.06)	111 (1.91)	0.92 (0.71-1.19)	0.5427	
BARC 5 bleeding					
Diabetes	6 (0.31)	5 (0.25)	0.81 (0.25-2.64)	0.7224	0.8034
Non-diabetes	18 (0.30)	17 (0.29)	0.96 (0.49-1.86)	0.9018	
BARC 3 bleeding					
Diabetes	45 (2.31)	49 (2.44)	1.06 (0.71-1.58)	0.7870	0.5126
Non-diabetes	114 (1.93)	101 (1.74)	0.90 (0.69-1.18)	0.4365	
Patient-oriented composite endpoint					
Diabetes	369 (18.72)	338 (16.66)	0.88 (0.76-1.02)	0.0955	0.4439
Non-diabetes	761 (12.79)	711 (12.17)	0.95 (0.85-1.05)	0.2911	
Net adverse clinical events					
Diabetes	397 (20.13)	366 (18.04)	0.89 (0.77-1.02)	0.1031	0.5431
Non-diabetes	839 (14.10)	778 (13.31)	0.94 (0.85-1.03)	0.1964	

BARC: bleeding academic research consortium, CI: confidence interval, HR: hazard ratio,

MI: myocardial infarction

Supplementary figure 1: two-year outcomes among non-diabetes, non-insulin treated and insulin-treated diabetes according to antiplatelet strategy

Outcomes at 2 years	Reference strategy, No. (%)	Experimental strategy, No. (%)	HR;exp/ref (95%CI)	P value	P value for interaction
All-cause death or new Q-wave MI					0.6420
Non-diabetes	222 (3.71)	202 (3.41)	0.92 (0.76-1.11)	0.3801	
Non-insulin treated diabetes	72 (5.32)	60 (4.23)	0.79 (0.56-1.11)	0.1767	
Insulin-treated diabetes	53 (8.59)	41 (6.77)	0.78 (0.52-1.17)	0.2312	
All-cause death					0.5678
Non-diabetes	157 (2.62)	145 (2.45)	0.93 (0.74-1.17)	0.5500	
Non-insulin treated diabetes	50 (3.69)	47 (3.31)	0.90 (0.60-1.33)	0.5870	
Insulin-treated diabetes	44 (7.13)	31 (5.12)	0.71 (0.45-1.12)	0.1388	
New Q-wave MI					0.2604
Non-diabetes	70 (1.18)	57 (0.98)	0.82 (0.58-1.17)	0.2728	
Non-insulin treated diabetes	24 (1.80)	14 (1.01)	0.55 (0.29-1.07)	0.0779	
Insulin-treated diabetes	9 (1.50)	12 (2.02)	1.35 (0.57-3.21)	0.4948	
Stroke overall					0.3566
Non-diabetes	47 (0.80)	49 (0.85)	1.06 (0.71-1.58)	0.7747	
Non-insulin treated diabetes	23 (1.74)	16 (1.15)	0.66 (0.35-1.25)	0.2043	
Insulin-treated diabetes	12 (2.01)	15 (2.52)	1.26 (0.59-2.70)	0.5442	
ischemic stroke					0.7830
Non-diabetes	40 (0.68)	35 (0.61)	0.89 (0.57-1.40)	0.6136	
Non-insulin treated diabetes	17 (1.28)	15 (1.08)	0.84 (0.42-1.68)	0.6223	
Insulin-treated diabetes	11 (1.85)	13 (2.19)	1.19 (0.53-2.66)	0.6664	
Hemorrhaghic stroke					0.1083
Non-diabetes	4 (0.07)	10 (0.17)	2.54 (0.80-8.10)	0.1150	
Non-insulin treated diabetes	4 (0.31)	1 (0.07)	0.24 (0.03-2.13)	0.1994	
Insulin-treated diabetes	1 (0.17)	2 (0.33)	2.03 (0.18-22.43)	0.5623	
Myocardial infarction					0.2049
Non-diabetes	168 (2.85)	158 (2.72)	0.96 (0.77-1.19)	0.6901	
Non-insulin treated diabetes	58 (4.37)	55 (3.94)	0.90 (0.63-1.31)	0.5917	
Insulin-treated diabetes	23 (3.88)	35 (5.92)	1.55 (0.92-2.62)	0.1032	
Any revascularization					0.6382
Non-diabetes	545 (9.25)	511 (8.84)	0.95 (0.84-1.07)	0.4068	
Non-insulin treated diabetes	159 (11.98)	156 (11.21)	0.93 (0.75-1.17)	0.5485	
Insulin-treated diabetes	86 (14.52)	70 (11.84)	0.81 (0.59-1.11)	0.1837	
Definite stent thrombosis					0.3334
Non-diabetes	49 (0.83)	46 (0.79)	0.95 (0.64-1.43)	0.8190	
Non-insulin treated diabetes	12 (0.90)	12 (0.85)	0.95 (0.43-2.12)	0.9036	
Insulin-treated diabetes	2 (0.33)	6 (1.01)	3.04 (0.61-15.04)	0.1737	
Definite or probable stent thrombosis					0.8040
Non-diabetes	60 (1.01)	59 (1.01)	1.00 (0.70-1.43)	0.9970	
Non-insulin treated diabetes	17 (1.27)	17 (1.20)	0.95 (0.49-1.86)	0.8836	
Insulin-treated diabetes	4 (0.66)	6 (1.01)	1.52 (0.43-5.37)	0.5187	
BARC 3 or 5 bleeding					0.3840
Non-diabetes	122 (2.06)	111 (1.91)	0.92 (0.71-1.19)	0.5427	
Non-insulin treated diabetes	32 (2.41)	30 (2.15)	0.89 (0.54-1.47)	0.6592	
Insulin-treated diabetes	15 (2.52)	22 (3.71)	1.49 (0.77-2.87)	0.2337	
BARC 5 bleeding					0.6287
Non-diabetes	18 (0.30)	17 (0.29)	0.96 (0.49-1.86)	0.9018	
Non-insulin treated diabetes	4 (0.30)	2 (0.14)	0.48 (0.09-2.60)	0.3924	
Insulin-treated diabetes	2 (0.34)	3 (0.51)	1.51 (0.25-9.03)	0.6522	
BARC 3 bleeding					0.4235
Non-diabetes	114 (1.93)	101 (1.74)	0.90 (0.69-1.18)	0.4365	
Non-insulin treated diabetes	31 (2.33)	29 (2.08)	0.89 (0.54-1.48)	0.6583	
Insulin-treated diabetes	14 (2.34)	20 (3.36)	1.45 (0.73-2.87)	0.2846	
Patient-oriented composite endpoint					0.7853
Non-diabetes	761 (12.79)	711 (12.17)	0.95 (0.85-1.05)	0.2911	
Non-insulin treated diabetes	234 (17.39)	218 (15.47)	0.88 (0.73-1.06)	0.1868	
Insulin-treated diabetes	132 (21.71)	118 (19.64)	0.90 (0.70-1.15)	0.3954	
Net adverse clinical events					0.7941
Non-diabetes	839 (14.10)	778 (13.31)	0.94 (0.85-1.03)	0.1964	
Non-insulin treated diabetes	254 (18.86)	235 (16.68)	0.87 (0.73-1.04)	0.1391	
Insulin-treated diabetes	140 (22.99)	129 (21.46)	0.93 (0.74-1.19)	0.5796	



BARC: bleeding academic research consortium, CI: confidence interval, HR: hazard ratio, MI: myocardial infarction, NACE; net adverse clinical events, POCE; patient-oriented composite endpoints.

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