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Impact of Platelet Glycoprotein IIb/IIIa Receptor Inhibitors on Outcomes of Diabetic Patients Undergoing Percutaneous Coronary Interventions Using Sirolimus-Eluting Stents

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Objective: We assessed the outcomes in diabetic patients undergoing percutaneous coronary intervention (PCI) using sirolimus-eluting stents (SES) as a function of treatment with glycoprotein (GP) IIb/IIIa inhibitors. Methods and Results: Of 551 diabetic patients treated with a SES in nine trials (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, REALITY, SVELTE, DIRECT, SIRIUS 2.25, and SIRIUS 4.0), 187 patients (33.9%) were administered GP IIb/IIIa inhibitors during PCI. GP IIb/IIIa blockade was associated with lower rates of myocardial infarction (MI) at 30 days (1.1% vs. 3.3%, *P* = 0.12) and at 1 year (1.1% vs. 4.7%, *P* = 0.04), and composite endpoint of cardiac death/MI at 1 year (2.2% vs. 6.2%, *P* = 0.05). Benefit from GP IIb/IIIa inhibitors was confined to 128 insulin-treated diabetics who had remarkable reduction in MI (0.0% vs. 6.3%, *P* = 0.04) and cardiac death/MI at 30 days (0.0% vs. 7.6%, *P* = 0.05) and at 1-year (0.0% vs. 13.4%, *P* = 0.01 and 0.0% vs. 15.7%, *P* = 0.0005, respectively). When treated with GP IIb/IIIa inhibitors, insulin-requiring diabetics had similar rates of 1-year death/MI when compared with the nondiabetic patients (0% vs. 4.7%, *P* = 0.13, respectively). There were no significant differences in outcomes as a function of GP IIb/IIIa blockade in diabetics not treated with insulin. Conclusion: In this analysis, outcomes of insulin requiring diabetic patients undergoing PCI with SES were considerably improved with adjunctive GP IIb/IIIa inhibitors by decreasing the rates of MI and composite endpoint of cardiac death/MI. © 2008 Wiley-Liss, Inc.

INTRODUCTION

Coronary artery disease is the major complication and leading cause of mortality in the diabetic population [1]. Percutaneous coronary interventions (PCI) in diabetic patients are associated with more frequent occurrence of restenosis and worse long-term clinical outcomes, including higher rates of mortality, myocardial infarction (MI), and repeat revascularization [2]. This is mainly because of diffuse atherosclerotic disease, prothrombotic and inflammatory state, endothelial cell dysfunction, and enhanced neointimal hyperplasia in response to vascular injury [3].

Adjunctive therapy with platelet glycoprotein (GP) IIb/IIIa receptor inhibitors is an established therapeutic modality for the prevention of early ischemic complications in high-risk patients undergoing PCI [4–6]. However, there has been ongoing debate whether GP IIb/IIIa inhibitors improve long-term prognosis of patients with diabetes mellitus treated with PCI. In the

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pooled analysis of three large-scale randomized PCI trials of abciximab versus placebo irrespective of the revascularization strategy (plain balloon angioplasty or stenting), monoclonal antibody fragment abciximab significantly reduced 6-month and 1-year rates of death, MI, and/or TVR in patients with diabetes [7]. Similarly, in the pooled analysis of six clinical trials assessing efficacy of intravenous GP IIb/IIIa inhibitors for the treatment of acute coronary syndromes, diabetic patients, especially if treated with PCI, had marked reduction in 30-day death and composite of death or MI [8]. Though, in the randomized abciximab versus placebo trial Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in diabetics (ISAR-SWEET), rates of survival and MI 1-year post-PCI in the entire diabetic cohort as well as in patients treated with insulin were not related to abciximab, while restenosis and TVR after bare metal stenting occurred significantly less frequently in low to moderate risk diabetic patients treated with abciximab [9].

Whether diabetic patients treated with sirolimus-eluting stents (SES) benefit from GP IIb/IIIa inhibitors is unknown. We therefore pooled the data from nine SES prospective trials to perform patient-level analysis of relationship between administration of GP IIb/IIIa inhibitors and outcomes of diabetic patients undergoing PCI with SES.

METHODS

In all included trials the patients were considered diabetic if they had a history of diagnosed diabetes mellitus recorded by site investigators at the time of patient enrollment; they were further stratified as insulin-requiring if insulin was listed among their medications. The study chart is presented in Fig. 1. Data on diabetic patients treated with PCI using SES were pooled from nine SES clinical trials including five randomized trials and four prospective nonrandomized studies. Outcomes were stratified by the use of GP IIb/IIIa inhibitors during PCI and type of diabetes treatment. The specific type of GP IIb/IIIa inhibitor used was not available in this analysis.

The authors were granted permission from Cordis Corporation, a Johnson & Johnson company for the performance of an unrestricted, patient-level pooled analysis. The data on all patients in each of the original study reports have been included and analyzed in this study. The protocols and principal results of the nine individual trials have been provided elsewhere [10–18]. Common inclusion criteria for all nine analyzed trials were patients with stable or unstable angina or inducible ischemia who underwent PCI with a

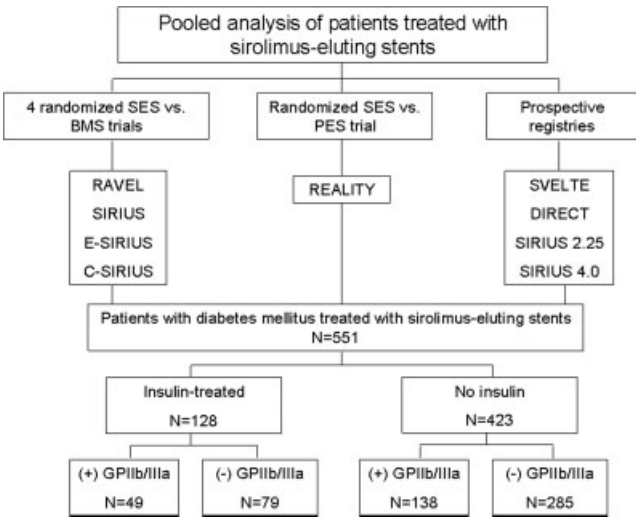

Fig. 1. Study chart design.

sirolimus-eluting Bx-Velocity stent (vs. a control stent in the randomized trials) for a de novo lesion (stenosis of 51–99% of the luminal diameter by visual assessment on baseline angiography) in a native coronary artery. Treatment of two lesions was allowed in the REALITY (only SES assigned patients were included in the analysis), and the use of more than one stent to cover the target lesion was allowed in E-SIRIUS, C-SIRIUS, and REALITY trials. In all the trials, predilatation of the lesion with a balloon was mandated per protocol, except for E-SIRIUS and C-SIRIUS (optional predilatation), as well as in the DIRECT trial (excluded by trial design). Creatine kinase (CK) and CK-MB were obtained 6–8, 12–16, and 18–24 hr after the procedure or before hospital discharge. The 12-lead electrocardiogram was obtained before and within 24 hr after the procedure or at the time of hospital discharge (whichever came first). In all trials, treatment with aspirin at a daily dose of 81–325 mg was started at least 12 hr preprocedure and continued indefinitely; a loading dose of 300 mg of clopidogrel was administered before or immediately after procedure. During the procedure, intravenous boluses of unfractionated heparin were administered to maintain an activated clotting time >250 sec. In all trials, treatment with GP IIb/IIIa inhibitors (abciximab, eptifibatide, or tirofiban) was at the discretion of the operator. Other data related to the included studies are summarized in Table I.

Although individual trial primary endpoints differed across the analyzed trials (Table I), the definition of all clinical endpoints was identical in each. MI was CK > 2X the upper limit of normal range accompanied by an elevated level of CK-MB in the absence or presence of new pathologic Q-waves on the electrocardiogram (for non-Q or Q-wave MI, respectively). Target

TABLE I. Summary of Trials Included into the Pooled Analysis

Study [references]	Study design	Patients in study	Primary endpoint	Diameter(s) of stents used (mm)	Lesion length (mm)	Diabetes	Duration of thienopyridine treatment	Time and completeness of angiographic follow-up
RAVEL [10]	Randomized double-blind	238	In-stent luminal late loss and MACE at 30 days, 6 and 12 months	2.5–3.5	<18	19%	2 months	6 months (90.8%)
SIRIUS [11]	Randomized double-blind	1,058	Target vessel failure (cardiac death, MI or TVR) at 270 days	2.5–3.5	15–30	26%	3 months	8 months (65.7%)
E-SIRIUS [12]	Randomized double-blind	352	In-stent minimal lumen diameter at 8 months	2.5–3.0	15–32	19%	2 months	8 months (88.6%)
C-SIRIUS [13]	Randomized double-blind	100	In-stent minimal lumen diameter at 8 months	2.5–3.0	15–32	24%	2 months	8 months (88.0%)
REALITY [14]	Randomized double-blind	1,386	Binary in-lesion restenosis at 8 months	2.25–3.0	>15 (1st lesion); 10 (2nd lesion)	28%	2 months	8 months (92.1%)
DIRECT [15]	Nonrandomized prospective	225	In-lesion late lumen loss at 8 months	2.5–3.5	15–30	31%	3 months	8 months (87.6%)
SVELTE [16]	Nonrandomized prospective	101	In-lesion late lumen loss at 8 mon	2.25–2.75	15–30	31%	3 months	8 months (94.1%)
SIRIUS 2.25 [17]	Nonrandomized prospective	100	In-lesion binary angiographic restenosis at 6 months	2.25	<20	40%	3 months	6 months (77.0%)
SIRIUS 4.0 [18]	Nonrandomized prospective	100	In-lesion late lumen loss at 6 months	4.0	<30	40%	3 months	6 months (90.0%)

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lesion revascularization (TLR) was any repeat PCI of the target lesion or bypass surgery of the target vessel that was performed for recurrent angina, ischemia, or diameter stenosis $\geq$70% by quantitative coronary angiography (QCA). Target vessel revascularization (TVR) was defined as any clinically driven repeat PCI of the target vessel or bypass surgery of the target vessel. Major adverse cardiac events (MACE) included death, MI, and TVR. In each trial, all clinical endpoints were adjudicated by an independent Clinical Events Committee.

Off-line quantitative angiographic measurements were performed by two independent angiographic core laboratories (Cardialysis, Rotterdam, The Netherlands, for the RAVEL and REALITY trials; Brigham and Women's Angiographic Core Laboratory, Boston, MA, for the other trials). Binary restenosis at angiographic follow-up was diameter stenosis >50%.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ 1 SD and compared using Student's *t*-test. Categorical data are presented as frequencies and percentages and compared using χ^2 tests or Fisher's exact test where appropriate.

Heterogeneity of the treatment effect on major outcomes across the randomized trials was tested using Cox's proportional hazards model with a study x IIb/IIIa GP inhibitors administered interaction term included, also controlling for baseline patient characteristics. The significance of the interaction term was evaluated using a likelihood ratio test.

Multivariable predictors of the composite endpoint of 1-year death and MI in diabetic patients were defined using logistic regression or Cox's proportional hazard model, with entry and exit criteria of $P < 0.05/0.1$. Two-sided 95% confidence intervals (CI) were constructed around each point estimate of hazards ratio (HR). We have assessed the function form of covariates and proportional hazards assumption using graphical and numerical methods based on the cumulative sums of martingale residuals and their transforms over certain coordinates. We found that the linear term was sufficient in the model, and there was no evidence of violation of the proportional hazards assumption. The following variables were included in the stepwise logistic regression: age, gender, history of MI, hypertension, multivessel coronary artery disease, unstable angina at presentation, ejection fraction, left anterior descending artery target vessel, lesion length, reference vessel diameter (RVD), calcification and/or thrombus on baseline coronary angiogram, and number of implanted stents and overlapping stents.

In-hospital outcomes were compared using χ^2 tests or Fisher's exact test, while out-of-hospital outcomes were summarized using Kaplan-Meier estimates and compared using log-rank tests. All tests were two-sided with a significance level of 0.05. *P*-values for multiple comparisons were not adjusted, and they should be viewed as hypothesis generating.

RESULTS

Clinical and Angiographic Characteristics at Baseline and Procedural Data

Of the 2,958 patients enrolled in the nine trials, 784 patients (26.5%) had diagnosed diabetes mellitus. A total of 551 diabetic patients were treated with a SES (19 in RAVEL, 131 in SIRIUS, 33 in E-SIRIUS, 12 in C-SIRIUS, 186 in REALITY, 27 in SVELTE, 70 in DIRECT, 40 in SIRIUS 2.25, and 33 in SIRIUS 4.0) including 128 patients requiring insulin and 423 patients treated with oral hypoglycemic medications and/or diet. A total of 187 diabetic patients (33.9%) were administered GP IIb/IIIa inhibitors. Proportion of diabetic patients that received GP IIb/IIIa inhibitors was none in RAVEL, 11.1% in SVELTE, 14.5% in REALITY, 21.2% in E-SIRIUS, 25.0% in SIRIUS 2.25, 33.3% in SIRIUS 4.0, 56.5% in SIRIUS, 58.3% in C-SIRIUS, and 68.6% in DIRECT trial.

Baseline clinical, angiographic, and procedural data of diabetic patients stratified by the use of GP IIb/IIIa inhibitors appear in Table II. Patients treated with GP IIb/IIIa inhibitors, compared to those who were not, more frequently had unstable angina, multivessel disease, lower ejection fraction, less frequent intervention on left anterior descending artery, more frequent intervention on the right coronary artery, and had bigger preprocedure RVD.

Patients treated with GP IIb/IIIa inhibitors had larger final RVD, minimal luminal diameter, and smaller percent diameter stenosis resulting in bigger acute gain, both in lesion and in stent. Rates of procedural success were not related to the use of GP IIb/IIIa inhibitors.

Clinical Outcomes

In-hospital, 30-day, and 1-year clinical events are presented in Table III. In-hospital clinical events were similar between diabetic patients that were administered GP IIb/IIIa inhibitors and those who were not. There was one case of acute stent thrombosis in a patient not treated with GP IIb/IIIa inhibitors. At 30-day follow-up, two more cases of stent thrombosis

TABLE II. Clinical and Angiographic Characteristics at Baseline and Procedural Data

Characteristics	Diabetic patients (−) GP IIb/IIIa $n = 364$	Diabetic patients (+) GP IIb/IIIa $n = 187$	P
Clinical characteristics			
Age, years	63.7 ± 10.3	63.4 ± 10.5	0.76
Male gender, *n* (%)	244 (67.0)	129 (69.0)	0.70
Hypertension, *n* (%)	278 (76.6)	143 (76.5)	1.00
Hyperlipidemia, *n* (%)	262 (72.2)	144 (78.7)	0.12
Current smoking, *n* (%)	65 (18.4)	125 (13.6)	0.18
Previous myocardial infarction, *n* (%)	133 (36.7)	53 (29.1)	0.08
Previous PCI, *n* (%)	118 (32.5)	55 (29.4)	0.50
Prior coronary bypass surgery, *n* (%)	39 (10.7)	25 (13.4)	0.39
Unstable angina, *n* (%)	161 (44.4)	140 (75.0)	<0.0001
Congestive heart failure, *n* (%)	29 (8.0)	15 (8.2)	1.00
Angiographic features			
Lesion length (mm)	15.04 ± 8.49	15.41 ± 7.74	0.59
Reference vessel diameter (mm)	2.47 ± 0.54	2.62 ± 0.53	0.001
Minimal luminal diameter (mm)	0.91 ± 0.34	0.96 ± 0.39	0.09
Diameter stenosis (%)	60.9 ± 11.0	63.7 ± 11.6	0.02
Left ventricle ejection fraction (%)	56.8 ± 12.5	54.1 ± 11.5	0.04
Target artery			
Left anterior descending artery	51.5	39.6	0.005
Left circumflex artery	23.3	26.6	0.37
Right coronary artery	24.5	32.9	0.03
Multivessel disease, *n* (%)	177 (49.5)	107 (58.1)	0.06
Procedural data			
Procedural success, *n* (%)	351 (96.7)	181 (96.8)	1.00
Stent length (mm)	22.1 ± 10.7	23.6 ± 9.7	0.13
Final reference-vessel diameter (mm)	2.47 ± 0.54	2.67 ± 0.54	<0.0001
Final minimal luminal diameter (mm)			
Analysis segment	1.97 ± 0.52	2.17 ± 0.56	<0.0001
In-stent	2.26 ± 0.50	2.46 ± 0.52	0.004
Final diameter stenosis (%)			
Analysis segment	22.0 ± 10.2	X19.4 ± 10.9	0.004
In-stent	11.7 ± 9.6	9.0 ± 8.9	0.0006
Acute gain (mm)			
Analysis segment	1.06 ± 0.47	1.21 ± 0.47	0.0002
In-stent	1.35 ± 0.46	1.50 ± 0.45	0.0002

Continuous data are expressed as mean ± SD. PCI, percutaneous coronary intervention.

occurred in patients not treated with GP IIb/IIIa inhibitors. There was one case of cardiac death in each of the treatment arms at 30-day follow-up. There was a trend toward lower rate of MI in patients treated with GP IIb/IIIa inhibitors compared to those who were not (2 patients and 12 patients, respectively), mainly due to lower frequency of non-Q-wave MI (2 patients and 11 patients, respectively). At 1-year follow-up, no additional cases of stent thrombosis occurred in either group, but there were five more cases of cardiac death, one more case of Q-wave MI, and three more cases of non Q-wave MI in patients not treated with GP IIb/IIIa inhibitors, and there was one more case of cardiac death in patients treated with GP IIb/IIIa inhibitors with no additional cases of MI. As a result, composite endpoint of cardiac death or MI occurred significant less frequently in patients treated with GP IIb/IIIa inhibitors.

Angiographic Follow-Up

Data on angiographic follow-up were available in 461 of 551 diabetic patients (83.7%), including 149 of 187 patients (79.7%) that were administered GP IIb/IIIa inhibitors and 312 of 364 patients (85.7%) who did not receive GP IIb/IIIa inhibitors ($P = 0.09$) (Table IV). RVD and minimal luminal diameter were bigger in patients treated with GP IIb/IIIa inhibitors. However, percent diameter stenosis, analysis segment late loss, and rates of binary angiographic restenosis both within the stent and within the segment were similar in the two groups.

Multivariable Analysis

The HR for death or MI during 1 year in a Cox's proportional hazards model for diabetic patients treated with GP IIb/IIIa inhibitors was 0.40 (95% CI;

TABLE III. In-Hospital, 30-Day, and 1-Year Clinical Outcomes in Diabetic Patients as a Function of Treatment with GP IIb/IIIa Inhibitors

	Diabetic patients		
Outcome	(−) GP IIb/IIIa $n = 364$	(+) GP IIb/IIIa $n = 187$	P
In-hospital			
All-cause death, *n* (%)	1 (0.3)	2 (1.1)	0.27
Cardiac death, *n* (%)	1 (0.3)	1 (0.5)	1.00
Myocardial infarction, *n* (%)	10 (2.7)	2 (1.1)	0.35
Q-wave	0 (0.0)	0 (0.0)	–
Non Q-wave	10 (2.7)	2 (1.1)	0.35
Cardiac death or myocardial infarction, *n* (%)	11 (3.0)	3 (1.6)	0.40
Stent thrombosis, *n* (%)	1 (0.3)	0 (0.0)	1.00
Target lesion revascularization, *n* (%)	1 (0.3)	1 (0.5)	1.00
Target vessel revascularization, *n* (%)	1 (0.3)	1 (0.5)	1.00
Major adverse cardiac events, *n* (%)	11 (3.0)	4 (2.1)	0.78
At 30-day follow-up			
All-cause death, *n* (%)	1 (0.3)	2 (1.1)	0.23
Cardiac death, *n* (%)	1 (0.3)	1 (0.5)	0.63
Myocardial infarction, *n* (%)	12 (3.3)	2 (1.1)	0.12
Q-wave	1 (0.3)	0 (0.0)	0.47
Non Q-wave	11 (3.0)	2 (1.1)	0.15
Cardiac death or myocardial infarction, *n* (%)	13 (3.6)	3 (1.6)	0.19
Stent thrombosis, *n* (%)	3 (0.8)	0 (0.0)	0.21
Target lesion revascularization, *n* (%)	3 (0.8)	1 (0.5)	0.71
Target vessel revascularization, *n* (%)	3 (0.8)	1 (0.5)	0.21
Major adverse cardiac events, *n* (%)	13 (3.6)	4 (2.1)	0.36
At 1-year follow-up			
All-cause death, *n* (%)	10 (3.5)	4 (2.2)	0.58
Cardiac death, *n* (%)	6 (1.9)	2 (1.1)	0.56
Myocardial infarction, *n* (%)	16 (4.7)	2 (1.1)	0.04
Q-wave	2 (0.7)	0 (0.0)	0.29
Non Q-wave	14 (4.0)	2 (1.1)	0.06
Cardiac death or myocardial infarction, *n* (%)	22 (6.2)	4 (2.2)	0.05
Stent thrombosis, *n* (%)	3 (0.8)	0 (0.0)	0.21
Target lesion revascularization, *n* (%)	28 (9.2)	13 (7.8)	0.56
Target vessel revascularization, *n* (%)	37 (12.8)	21 (12.4)	0.96
Major adverse cardiac events, *n* (%)	47 (15.1)	20 (11.5)	0.30

TABLE IV. Angiographic Findings at Follow-Up

	Diabetic patients		
Characteristics	(−) GP IIb/IIIa $n = 312$	(+) GP IIb/IIIa $n = 149$	P
Reference vessel diameter (mm)	2.52 ± 0.53	2.63 ± 0.48	0.02
Minimal luminal diameter (mm)			
Analysis segment	1.78 ± 0.63	1.90 ± 0.70	0.05
In stent	2.03 ± 0.68	2.18 ± 0.74	0.02
Diameter stenosis (%)			
Analysis segment	30.9 ± 17.5	28.6 ± 20.5	0.20
In stent	21.6 ± 20.2	18.2 ± 22.2	0.10
Late loss (mm)			
Analysis segment	0.19 ± 0.45	0.24 ± 0.50	0.25
In stent	0.22 ± 0.50	0.26 ± 0.52	0.36
Binary restenosis rate (%)			
Analysis segment	15.5%	12.7%	0.43
In stent	9.9%	8.5%	0.75

Continuous data are expressed as mean ± SD.

TABLE V. Baseline Characteristics and Clinical Outcomes of Patients Stratified by Diabetes Treatment and Use of GP IIb/IIIa Inhibitors

	Insulin-treated diabetic patients			Diabetic patients not on insulin		
	(−) GP IIb/IIIa $n = 79$	(+) GP IIb/IIIa $n = 49$	P	(−) GP IIb/IIIa $n = 285$	(+) GP IIb/IIIa $n = 138$	P
Age (years)	63.4 ± 11.5	64.3 ± 11.9	0.68	63.7 ± 10.0	63.1 ± 9.9	0.52
Male gender, *n* (%)	44 (55.7%)	30 (61.2%)	0.58	200 (70.2%)	99 (71.7%)	0.82
Left ventricle ejection fraction (%)	55.3 ± 10.7	54.0 ± 13.2	0.64	57.2 ± 12.9	54.2 ± 10.9	0.04
Left anterior descending artery target vessel (%)	52.1%	41.8%	0.24	51.4%	38.8%	0.01
Multivessel disease, *n* (%)	35 (44.3%)	26 (53.0%)	0.36	142 (49.8%)	81 (59.1%)	0.51
Lesion length (mm)	15.07 ± 8.88	16.03 ± 9.38	0.54	15.04 ± 8.39	15.18 ± 7.06	0.85
Reference vessel diameter (mm)	2.39 ± 0.52	2.49 ± 0.48	0.21	2.50 ± 0.55	2.67 ± 0.54	0.001
Minimal luminal diameter (mm)	0.95 ± 0.30	0.92 ± 0.32	0.53	0.90 ± 0.35	0.98 ± 0.41	0.03
Diameter stenosis (%)	59.7 ± 10.6	63.2 ± 11.3	0.07	63.8 ± 11.3	63.5 ± 12.2	0.78
Total stented segment length (mm)	22.6 ± 10.6	25.4 ± 10.3	0.16	22.0 ± 10.7	22.9 ± 9.5	0.39
In-hospital outcomes						
All-cause death (%)	1 (1.3)	0 (0.0)	1.00	0 (0.0)	2 (1.4)	0.11
Cardiac death (%)	1 (1.3)	0 (0.0)	1.00	0 (0.0)	1 (0.7)	0.33
Myocardial infarction (%)	5 (6.3)	0 (0.0)	0.15	5 (1.8)	2 (1.4)	1.00
Q-wave	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
Non Q-wave	5 (6.3)	0 (0.0)	0.15	5 (1.8)	2 (1.4)	1.00
Stent thrombosis (%)	1 (1.3)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	–
Target lesion revascularization (%)	1 (1.3)	0 (0.0)	1.00	0 (0.0)	1 (0.7)	0.33
Cardiac death or myocardial infarction (%)	6 (7.6)	0 (0.0)	0.08	5 (1.8)	3 (2.2)	0.72
Target vessel revascularization (%)	1 (1.3)	0 (0.0)	1.00	0 (0.0)	1 (0.7)	0.33
Major adverse cardiac events (%)	6 (7.6)	0 (0.0)	0.08	5 (1.8)	4 (2.9)	0.48
Outcomes at 30-day follow-up						
All-cause death (%)	1 (1.3)	0 (0.0)	0.43	0 (0.0)	2 (1.4)	0.04
Cardiac death (%)	1 (1.3)	0 (0.0)	0.43	0 (0.0)	1 (0.7)	0.15
Myocardial infarction (%)	5 (6.3)	0 (0.0)	0.07	7 (2.5)	2 (1.4)	0.51
Q-wave	0 (0.0)	0 (0.0)	–	1 (0.4)	0 (0.0)	0.49
Non Q-wave	5 (6.3)	0 (0.0)	0.07	6 (2.1)	2 (1.4)	0.64
Cardiac death or myocardial infarction (%)	6 (7.6)	0 (0.0)	0.05	7 (2.5)	3 (2.2)	0.86
Stent thrombosis (%)	1 (1.3)	0 (0.0)	0.43	2 (0.7)	0 (0.0)	0.33
Target lesion revascularization (%)	1 (1.3)	0 (0.0)	0.43	2 (0.7)	1 (0.7)	0.97
Target vessel revascularization (%)	1 (1.3)	0 (0.0)	0.43	2 (0.7)	0 (0.0)	0.33
Major adverse cardiac events (%)	6 (7.6)	0 (0.0)	0.05	7 (2.5)	4 (2.9)	0.78

0.15–1.04, $P = 0.059$). Target lesion length was the only significant predictor of death or MI at 1 year (HR = 1.04; 95% CI; 1.02–1.08, $P = 0.02$). We also included an interaction term for study x GP IIb/IIIa administration in the multivariable model which was not statistically significant.

Glycoprotein IIb/IIIa Inhibitors and Outcomes of Diabetic Patients Treated With Insulin

Among insulin-treated diabetics, patients who received GP IIb/IIIa inhibitors compared to those who did not more frequently had unstable angina as an indication for PCI (73.1% vs. 38.5%, respectively, $P = 0.008$). Other characteristics were quite similar including preprocedure RVD (2.49 ± 0.48 mm vs. 2.39 ± 0.52 mm, $P = 0.21$), lesion length (16.0 ± 9.4 mm vs. 15.1 ± 8.9 mm, $P = 0.54$), and total stented segment length (25.4 ± 10.4 mm vs. 22.6 ± 10.6 mm, $P = 0.16$). In-hospital and 30-day outcomes stratified by diabetes treatment type and administration of GP IIb/IIIa inhibitors during PCI are shown in Table V. Treatment with GP IIb/IIIa inhibitors was associated with the absence of any event, translating into a trend toward lower rate of non-Q-wave MI and with significantly lower rates of composite endpoint of cardiac death or MI and MACE. Other 30-day clinical endpoints occurred with similar frequency in the two groups.

One-year clinical events appear in Fig. 2A. Patients treated with GP IIb/IIIa inhibitors had remarkably lower rates of all-cause death, cardiac death, MI, composite endpoint of cardiac death or MI, and MACE. Difference in the incidence of MI was driven mainly by less frequent occurrence of non-Q-wave MI in patients treated with GP IIb/IIIa inhibitors. One-year survival free from MI was significantly higher in patients treated versus not treated with GP IIb/IIIa inhibitors (Fig. 2B).

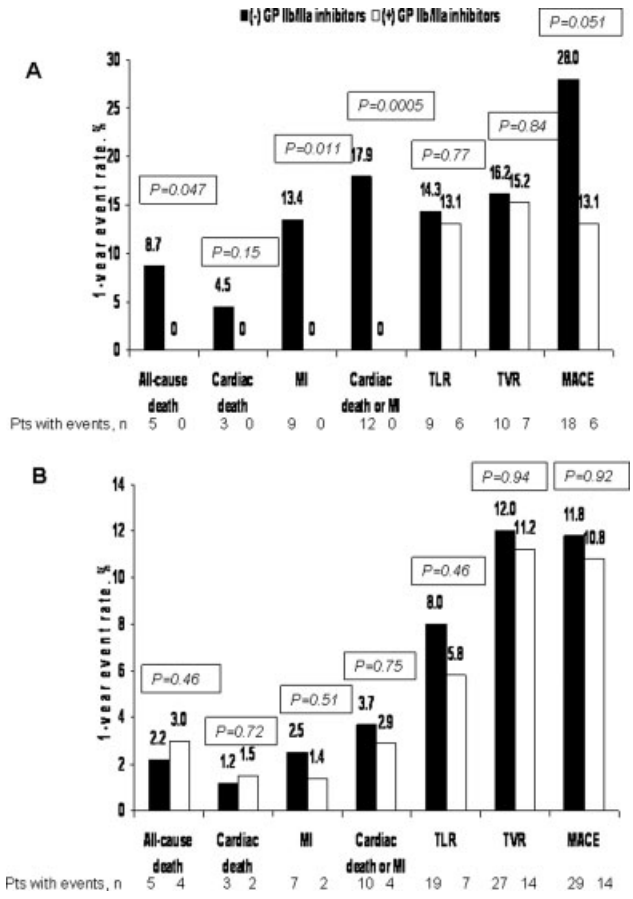

Fig. 2. One-year MACE in diabetic patients treated with insulin (A) and not requiring insulin (B) stratified by administration of GP IIb/IIIa inhibitors.

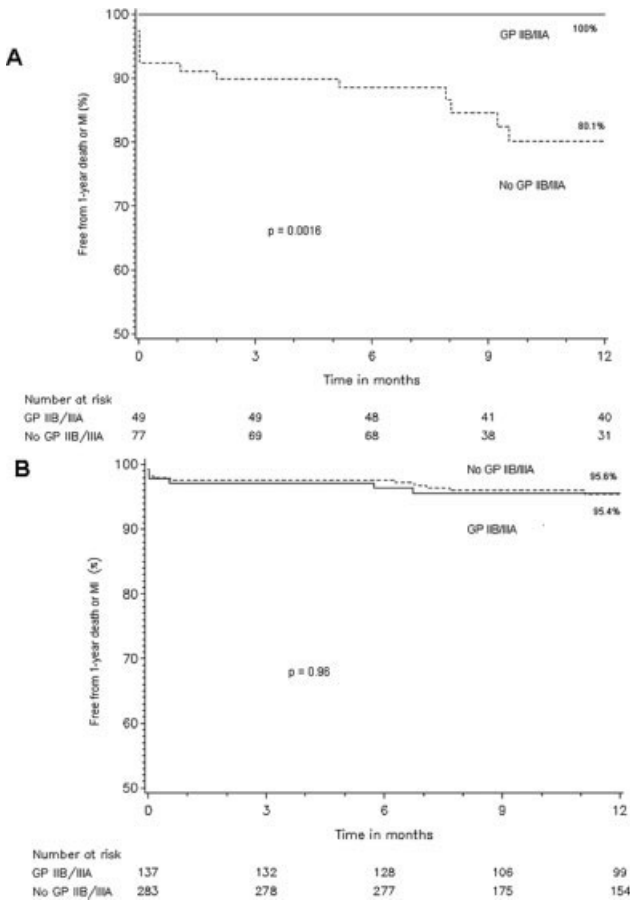

Fig. 3. Cumulative risk of 1-year death and/or myocardial infarction in insulin-treated diabetic patients (A) and diabetic patients not treated with insulin (B) stratified by administration of GP IIb/IIIa inhibitors.

Rates of binary angiographic in-lesion restenosis in patients requiring insulin were not related to treatment with GP IIb/IIIa inhibitors (20.9% vs. 20.5%, $P = 1.00$).

Glycoprotein IIb/IIIa Inhibitors and Outcomes of Diabetic Patients Not Requiring Insulin

Among diabetics not requiring insulin, patients who were administered GP IIb/IIIa inhibitors compared to those who were not had a higher frequency of unstable angina as an indication for PCI (75.8% vs. 46.1%, $P < 0.0001$), lower frequency of prior MI (26.9% vs. 38.5%, $P = 0.021$), left anterior descending artery target vessel (38.3% vs. 51.4%, $P = 0.011$), and baseline TIMI flow grade 0–2 (7.9% vs. 14.5%, $P = 0.053$), and had larger preprocedure RVD (2.67 ± 0.54 mm vs. 2.50 ± 0.55 mm, $P = 0.001$). Target lesion length (15.2 ± 7.1 mm vs. 15.0 ± 8.4 mm, $P = 0.85$) and total stented segment length (22.9 ± 9.5 mm vs. 22.0 ± 10.7 mm, $P = 0.39$) were not related to the treatment with GP IIb/IIIa inhibitors. As shown in Table V and Fig. 3A, there were no significant differences in early and late clinical outcomes as a function of treatment with GP IIb/IIIa inhibitors. One-year survival free from MI was also not related to GP IIb/IIIa inhibitors (Fig. 3B).

Rates of binary angiographic in-lesion restenosis in patients not requiring insulin did not differ among patients treated or not treated with GP IIb/IIIa inhibitors (9.8% vs. 14.2%, $P = 0.26$).

Testing for the heterogeneity of the GP IIb/IIIa inhibitors treatment effect using multivariable models with and without study × treatment interaction term, and adjustment for significant baseline characteristics showed that the interaction term was not significant from the likelihood ratio test ($P = 0.84$, $P = 0.15$, and $P = 0.34$ for 1-year death, MI, and composite endpoint of cardiac death or MI, respectively). Therefore, the treatment effect was homogeneous across all studies.

DISCUSSION

There are two main findings of the present pooled analysis, which assesses the impact of treatment with GP IIb/IIIa inhibitors on outcomes of patients with diabetes mellitus undergoing coronary revascularization using SES: (1) In the entire diabetic cohort, treatment with GP IIb/IIIa inhibitors was associated with lower rates of MI and composite endpoint of cardiac death or MI; and (2) Benefit from GP IIb/IIIa inhibitors in reducing rates of MI and composite endpoint of cardiac death or MI at 30 days and at 1 year was confined to insulin-treated diabetic patients, while patients not on insulin did not show a significant advantage from GP IIb/IIIa blockade.

Previous studies demonstrated convincingly that diabetes is a powerful predictor of adverse outcome after either surgical or percutaneous revascularization including higher rates of mortality, MI, and additional revascularization procedures at follow-up [2]. In this analysis, adjunctive therapy with GP IIb/IIIa inhibitors in diabetic patients undergoing PCI using SES was associated with a remarkable reduction in the firm ischemic endpoint of cardiac death or MI at 1 year. The outcomes were driven both by excess of MI (mainly non-Q-wave) and cardiac death in patients not treated with GP IIb/IIIa inhibitors. Likewise, in a pooled analysis from three randomized abciximab versus placebo PCI trials, reduction in 1-year mortality, non-Q-wave MI, and MACE was limited to insulin-requiring diabetics [7]. The plausible explanations of how post-PCI myocardial necrosis diagnosed by CK-MB elevation worsens the long-term prognosis of patients treated with PCI are not known, and probably include the susceptibility to ventricular arrhythmias via microreentry mechanism, development of heart failure, and compromise of coronary collaterals by microembolization. The data from the mentioned pooled analysis generated hypothesis that non-GP IIb/IIIa properties of abciximab, such as vitronectin or Mac-1 receptor inhibition, may also favorably affect late mortality [7]. However, in the later head-to-head comparison of two platelet GP IIb/IIIa inhibitors as adjunctive treatment for patients treated with stent-assisted PCI, administration of the small-molecule tirofiban and the antibody fragment abciximab was associated with similar outcomes including 1-year mortality among diabetic patients, suggesting that the non-GP IIb/IIIa properties of abciximab have questionable long-term clinical benefit in these patients [19].

Our results are in contrast to the data of ISAR-SWEET trial that did not support a significant impact of abciximab on the risk of death and MI within 1 year in diabetic patients undergoing PCI after pretreatment with a 600 mg loading dose of clopidogrel [9]. In all trials included into our analysis, loading regimen of clopidogrel (300 mg) differed from one used in the ISAR-SWEET, that might explain in part the diverge outcomes. It is also possible that treatment of diabetic patients with bare-metal and drug-eluting stents with/without GP IIb/IIIa inhibitors has different effect on outcomes. Furthermore, the influence of possible differences in unmeasured patients' and lesions' characteristics cannot be excluded to explain entirely the diversity of results.

In our analysis, some angiographic characteristics and acute procedural outcomes were more favorable in patients treated with GP IIb/IIIa inhibitors compared to those who were not including less frequent intervention on left anterior descending artery, bigger RVD, smaller final diameter stenosis, and bigger acute gain. However, the patients with insulin-treated diabetes, who in fact benefited from treatment with GP IIb/IIIa inhibitors, had quite similar characteristics including angiographic and procedural features. Moreover, unstable angina as indication for PCI known to have negative impact on clinical outcomes was almost twice as common in insulin-requiring diabetics treated with GP IIb/IIIa inhibitors compared to those who were not. In our study, none of the patients requiring insulin, if treated with GP IIb/IIIa inhibitors, developed MI or died during 1 year post-PCI. Also of note, the association between GP IIb/IIIa blockade and lower rates of cardiac death and MI observed during the early phase after administration of GP IIb/IIIa inhibitors (in-hospital and at 30 days) persisted at 1-year follow-up and, in fact, was even more prominent. Remarkably, in the cohort that was administered GP IIb/IIIa inhibitors, the 1-year rates of hard clinical endpoints for insulin-requiring diabetics were comparable to that of nondiabetic patients (0% vs. 0.8% for death, $P = 0.54$; 0% vs. 4.7% for MI, $P = 0.13$; and 0% vs. 4.7% for death/MI, $P = 0.13$, respectively).

Possible mechanisms of the benefit of GP IIb/IIIa blockade in insulin-dependent diabetic patients include but are not limited to decrease in platelet aggregation and adhesion, improvement in microvascular function and coronary flow reserve, prevention of distal embolization, and attenuation of the response of the endothelium to mechanical injury in the presence of diffusely diseased vasculature [20–23]. An increased number of GP Ib and GP IIb/IIIa receptors per platelet and exaggerated platelets activation typical to diabetes may have increased the potency of a IIb/IIIa blockade [24,25]. Some studies also suggest that GP IIb/IIIa inhibitors exhibit anti-inflammatory properties and may play a role in modulating plaque stability [26,27]. Vascular inflammation is prominent in diabetic patients [28]. Abciximab has been shown to decrease the magnitude of rise in systemic anti-inflammatory markers

(C-reactive protein, interleukin-6, and tumor necrosis factor-α) post-PCI [26]. Reduction of circulating soluble CD40 ligand and the formation of leukocyte–platelet aggregates in patients with acute coronary syndromes was documented after treatment with abciximab and eptifibatide [27].

In this report, no beneficial effect of GP IIb/IIIa inhibitors was apparent with relation to angiographic and clinical restenosis. This is in contrast to the findings of the ISAR-SWEET trial [9] but in agreement with the findings of two other randomized studies, in which treatment with abciximab in diabetic patients undergoing bare metal stent implantation was not associated with a reduction of in-stent neointimal hyperplasia as assessed by intravascular volumetric analysis and/or QCA [29,30].

Study Limitations

This post hoc analysis was not prespecified, and should thus be considered hypothesis generating, and complementary to large, prospectively collected databases. Given the post hoc nature of this patient-level pooled analysis, it lacks data on diabetes status including duration and type of diabetes, glycemic control, and the presence of proteinuria known to affect long-term prognosis in the diabetic population [31]. The study sample of insulin-requiring patients is fairly small. None of the included trials was powered to determine differences in restenosis and clinical events in patients with relation to diabetes type or use of GP IIb/IIIa inhibitors; therefore, obtained data (either positive or negative) may be due to chance alone (type I error). Treatment with GP IIb/IIIa inhibitors was left to the operator discretion, and may be associated with confounding factors not included into the multivariable analysis. Given the lack of information on the type of GP IIb/IIIa inhibitor used, the effect of drug class on outcomes has been assessed. The data on the cardiac markers and timing of clopidogrel loading dose were also not available for this analysis. Also, no data are available with regard to the continuation of clopidogrel beyond the recommended by trials duration of therapy. Finally, the results of this pooled analysis apply only to SES and should not be extrapolated to other drug-eluting stents.

CONCLUSION

In this first report on the impact of GP IIb/IIIa blockade in patients with diabetes mellitus undergoing PCI using SES, short- and long-term outcomes were improved considerably in insulin-requiring diabetics by decreasing the rates of MI and composite endpoint of cardiac mortality or MI. Our results indicate that if PCI using SES is performed in this diabetic subset, GP IIb/IIIa inhibition should be strongly considered as part of the procedural pharmacotherapy to improve outcomes in these patients. Given the diffuse and progressive nature of coronary atherosclerosis in diabetic patients and an accepted technique of the usage of longer drug-eluting stents to avoid incomplete coverage of diseased segments to prevent restenosis, the use of GP IIb/IIIa inhibitors may be a valuable treatment modality to reduce periprocedural MI and improve prognosis in this population. Large-scale randomized study is warranted to further evaluate the impact of GP IIb/IIIa inhibitors on prognosis of diabetic patients treated with SES. Findings of this analysis suggest that such assessment should be performed with relation to diabetes treatment modality.

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