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Everolimus-eluting versus sirolimus-eluting coronary stents in patients with and without diabetes mellitus

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KEYWORDS

- diabetes mellitus
- drug-eluting stents
- percutaneous coronary intervention

Abstract

Aims: Patients with diabetes mellitus have a higher risk of adverse events after percutaneous coronary intervention (PCI). This study aimed to elucidate the relative efficacy of everolimus-eluting stents (EES) versus sirolimus-eluting stents (SES) according to diabetic status.

Methods and results: Data from the EXCELLENT randomised trial and registry were pooled in a per protocol analysis manner. The primary endpoint was target lesion failure (TLF), a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularisation. Among a total of 6,524 patients, 2,404 (36.8%) had diabetes mellitus. Patients with diabetes were shown to have a higher rate of TLF after PCI, which was mainly driven by differences in cardiac death and myocardial infarction, while the rate of repeat revascularisation and stent thrombosis did not differ significantly. TLF occurred at a similar rate between patients treated with EES versus SES in each subgroup stratified by diabetic status (interaction p=0.384). In addition, no significant interactions were present with regard to any pre-specified clinical endpoints. The results were corroborated by analysis with inverse probability of treatment weighting (interaction p=0.329). We also found that insulin-dependent diabetes imposed an even greater risk of TLF on patients treated with PCI.

Conclusions: Despite the recent advances in drug-eluting stent technology, diabetic patients are still at higher risk of adverse clinical events after PCI than those without diabetes mellitus. Whether a patient was treated with EES or SES had no significant interaction with diabetic status in terms of clinical outcome after PCI.

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Introduction

Patients with diabetes mellitus are prone to a higher incidence of adverse clinical events as well as angiographic restenosis after percutaneous coronary intervention (PCI)[1,2]. Despite the development of drug-eluting stents (DES), which have been shown to reduce the need for repeat revascularisation compared to bare metal stents in patients with diabetes mellitus[3-5], diabetes still remains one of the major predictors for poor clinical outcomes[6-8]. The selection of optimal DES providing the best performance is one of the main issues in the treatment of diabetic patients with coronary artery disease.

Previous studies have proven an interaction between the performance of different types of DES and diabetic status. Everolimus-eluting stents (EES), when compared to paclitaxel-eluting stents, were shown to reduce the risk of adverse outcomes among patients without diabetes mellitus significantly. Meanwhile, diabetic patients showed no significant differences in terms of safety and efficacy outcomes when treated with EES or paclitaxel-eluting stents[9,10]. Although controversial, studies comparing sirolimus-eluting stents (SES) versus paclitaxel-eluting stents also suggested the attenuation of antirestenotic effects of SES in diabetic subgroups[11-13]. So far, the question as to whether different types of limus-eluting stents, namely EES compared to SES, have relative efficacy according to diabetic status in terms of clinical outcomes after PCI has not been fully investigated. To address this issue, we compared one-year clinical outcomes after implantation of EES versus SES in patients with and without diabetes mellitus.

Methods

PATIENTS

For the purpose of this study, we pooled the database from the EXCELLENT randomised trial and the non-randomised all-comers EXCELLENT registry with the agreement of both steering committees. The Efficacy of Xience/promus versus Cypher in rEducing Late Loss after stENTing (EXCELLENT) trial was a prospective, randomised, multicentre trial which enrolled 1,443 patients between June 2008 and July 2009 in order to compare the efficacy of EES versus SES in reducing late loss in patients undergoing PCI. The study design and the primary results have been reported previously[14-16]. The EXCELLENT registry was an open-label, multicentre, all-comers registry where consecutive patients receiving EES were prospectively enrolled between May 2008 and May 2010 while a historical control of consecutive patients who received SES between January 2004 and April 2009 was retrospectively registered from 29 centres in Korea. The patients enrolled in the EXCELLENT registry were completely distinct from those enrolled in the EXCELLENT randomised trial[17]. Patients were considered as having diabetes mellitus if they had a history of diabetes diagnosed and/or treated by a healthcare provider. Diabetic status was classified as insulin-dependent if the patient was taking insulin, or non-insulin-dependent if he/she was taking only oral hypoglycaemic agents or treated with diet therapy.

The study protocols were approved by the ethics committee at each participating centre, and followed the principles of the Declaration of Helsinki. All patients provided written, informed consent for participation in the trial. Patients were grouped into the EES and SES groups on a per protocol basis. The study scheme is summarised in **Figure 1**.

STUDY ENDPOINTS

The primary analysis endpoint of the present study was target lesion failure (TLF), a composite of cardiac death, target vessel-related myocardial infarction (MI), and clinically-driven target lesion revascularisation (TLR) at one year. Secondary endpoints included all-cause death, cardiac death, all-cause MI, target vessel-related MI, target vessel revascularisation (TVR), TLR, and stent thrombosis. All definitions of clinical events followed the consensus of the Academic Research Consortium (ARC)[18]. Specifically, cardiac death was defined as any death due to a cardiac cause, unwitnessed death and death of unknown cause, and all procedure-related deaths. MI included those occurring during the immediate periprocedural period (within 48 hours after PCI) and longer after the procedure (more than 48 hours after PCI). Whether MI was related to target vessel or not was adjudicated on the basis of angiographic and/or electrocardiographic data. TLR was defined as any repeat percutaneous or surgical intervention of the target lesion, which means the treated segment from 5 mm proximal to the stent and up to 5 mm distal to the stent. The occurrence of "definite" and "probable" stent thrombosis (ST), according to ARC definition, was recorded. Target vessel failure was defined as a composite of cardiac death, target vessel-related MI, and clinically-driven TLR, while a major adverse cardiovascular event was as a composite of all-cause death, all-cause MI, TVR, and ST. Clinical events were adjudicated by an independent adjudication committee in both the EXCELLENT trial and the EXCELLENT registry.

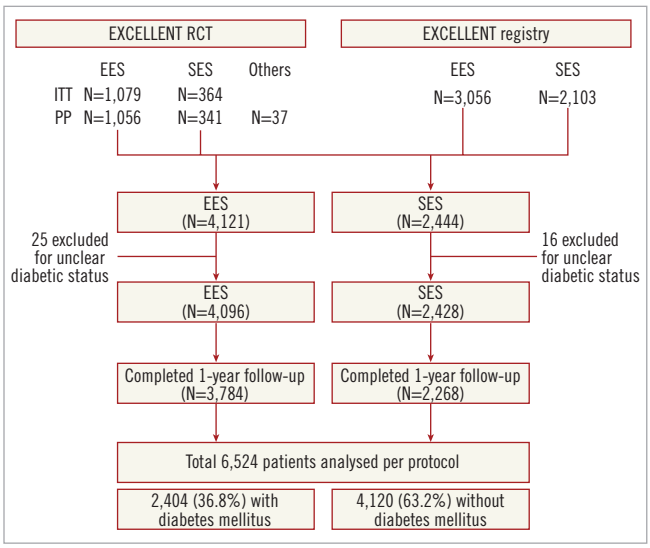

Figure 1. *Study protocol. EES: everolimus-eluting stent; ITT: intention-to-treat; PP: per protocol; RCT: randomised controlled trial; SES: sirolimus-eluting stent*

Table 1. Baseline characteristics.

	Patients with diabetes mellitus (N=2,404)			Patients without diabetes mellitus (N=4,120)		
	EES (N=1,545)	SES (N=859)	*p*-value	EES (N=2,551)	SES (N=1,569)	*p*-value
Demographic & clinical variables						
Age - years	64.3±9.7	63.9±9.6	0.328	63.1±11.2	61.7±11.2	<0.001
Male	999 (64.7)	555 (64.6)	0.980	1,729 (67.8)	1,101 (70.2)	0.108
Body mass index - kg/m^2	25.0±3.6	24.8±3.5	0.146	24.7±3.3	24.7±3.3	0.707
Hypertension	1,175 (76.1)	600 (69.8)	0.001	1,577 (61.8)	841 (53.6)	<0.001
Dyslipidaemia	766 (49.6)	392 (45.6)	0.064	1,125 (44.1)	589 (37.5)	<0.001
Current smoking	379 (24.5)	232 (27.0)	0.181	782 (30.7)	519 (33.1)	0.104
Chronic renal failure	78 (5.0)	44 (5.1)	0.937	38 (1.5)	14 (0.9)	0.095
Peripheral artery disease	32 (2.1)	16 (1.9)	0.726	29 (1.1)	16 (1.0)	0.726
Previous cerebrovascular disease	141 (9.1)	71 (8.3)	0.476	168 (6.6)	84 (5.4)	0.109
Previous myocardial infarction	110 (7.1)	77 (9.0)	0.106	155 (6.1)	156 (9.9)	<0.001
Congestive heart failure	30 (1.9)	20 (2.3)	0.525	40 (1.6)	13 (0.8)	0.041
Family history of coronary artery disease	96 (6.2)	38 (4.4)	0.067	172 (6.7)	90 (5.7)	0.199
Left ventricular ejection fraction - %	59.4±11.3	58.2±12.2	0.025	60.1±10.8	60.1±11.3	0.965
Clinical indication			<0.001			<0.001
Silent ischaemia	65 (4.2)	31 (3.7)		71 (2.8)	40 (2.6)	
Stable angina	622 (40.4)	315 (37.3)		926 (36.5)	526 (34.3)	
Unstable angina	574 (37.3)	291 (34.5)		991 (39.1)	529 (34.5)	
Non-ST-elevation myocardial infarction	153 (9.9)	77 (9.1)		265 (10.4)	170 (11.1)	
ST-elevation myocardial infarction	126 (8.2)	130 (15.4)		284 (11.2)	267 (17.4)	
Angiographic variables						
Extent of disease			0.357			0.064
Single-vessel disease	592 (38.4)	348 (40.6)		1,323 (51.9)	763 (48.8)	
Two-vessel disease	506 (32.9)	258 (30.1)		753 (29.6)	515 (32.9)	
Three-vessel disease	442 (28.7)	252 (29.4)		471 (18.5)	285 (18.2)	
Number of lesions	1.5±0.7	1.5±0.8	0.932	1.4±0.7	1.4±0.7	0.347
Left main coronary artery lesion	69 (4.5)	49 (5.7)	0.178	105 (4.1)	81 (5.2)	0.116
Thrombus	128 (8.3)	79 (9.2)	0.445	257 (10.1)	139 (8.9)	0.199
Previously treated lesions	100 (6.5)	89 (10.4)	0.001	128 (5.0)	158 (10.1)	<0.001
Bifurcation lesion	265 (17.2)	140 (16.3)	0.592	423 (16.6)	243 (15.5)	0.354
Number of stents per patient	1.6±0.9	1.6±0.9	0.286	1.5±0.8	1.5±0.8	0.266
Maximal stent diameter - mm	3.14±0.43	3.08±0.37	<0.001	3.21±0.45	3.15±0.37	<0.001
Total stent length - mm	37.1±24.4	41.5±26.2	<0.001	33.7±22.4	35.9±21.6	0.002
Discharge medications						
Aspirin	1,497 (97.2)	843 (98.4)	0.074	2,500 (98.0)	1,545 (98.7)	0.138
Clopidogrel	1,500 (97.4)	831 (97.0)	0.531	2,502 (98.1)	1,532 (97.8)	0.520
β-blockers	956 (62.1)	560(65.3)	0.112	1,014 (39.8)	564 (36.0)	0.016
ACE inhibitors	533 (34.6)	342 (39.9)	0.010	920 (36.1)	612 (39.1)	0.053
Angiotensin receptor antagonist	530 (34.4)	308 (35.9)	0.453	757 (29.7)	4,741 (30.1)	0.790
Statins	1,283 (83.3)	701 (81.8)	0.347	2,185 (85.7)	1,269 (81.0)	<0.001
Calcium channel blockers	464 (30.1)	259 (30.2)	0.963	720 (28.2)	1,108 (70.8)	0.486
Oral hypoglycaemic agents	873 (56.7)	456 (53.2)	0.100	47 (1.8)	28 (1.8)	0.898
Insulin	153 (9.9)	73 (8.5)	0.255	4 (0.2)	5 (0.3)	0.279

EES: everolimus-eluting stent; SES: sirolimus-eluting stent

STATISTICAL ANALYSIS

Clinical outcomes were compared between patients treated with EES versus SES stratified by the presence of diabetes mellitus. Baseline data were presented as frequencies or mean±SD. Categorical variables were compared with the use of the χ^2 test or Fisher's exact test, and continuous variables with the Student's t-test. The event-free survival rates were analysed by the Kaplan-Meier method, and the differences in survival curves between the groups were assessed with the log-rank test. Interaction was tested with use of the Cox proportional hazards model to determine whether the presence of diabetes mellitus had an effect on the relative risk of EES versus SES regarding any clinical endpoints.

In order to minimise selection bias in this study, weighted Cox proportional hazards regression models using the inverse probability of treatment weights (IPTW) was used[19]. Propensity to the treatment with EES compared to SES was scored by the use of multivariable logistic regression for every patient with 24 clinical and angiographic variables, such as sex, age, body mass index, hypertension, dyslipidaemia, smoking status, the presence of peripheral artery disease, family history of coronary artery disease, clinical diagnosis, previous PCI, previous bypass surgery, history of myocardial infarction, congestive heart failure, chronic renal failure, ejection fraction estimated with echocardiography, extent of diseased coronary artery, stent diameter, total stent length, number of lesions, number of implanted stents, left main coronary artery disease, bifurcation lesion, and the presence of thrombus. A multiple imputation method was used to fill out missing variables with the assumption that data were missing completely at random. No interactions were considered in the model. Propensity scores were used to derive the IPTW, with the inverse of the propensity score for patients treated with EES and the inverse of (1 - propensity score) for patients with SES. Clinical outcomes were compared with the use of logistic regression models adjusted with the inverse probability of treatment weighting. A two-sided p-value less than 0.05 was considered significant for all tests. All statistical analyses were performed using IBM SPSS version 18.0 (IBM Corp., Armonk, NY, USA).

Results

PATIENT CHARACTERISTICS

The study and analysis scheme is shown in **Figure 1**. As shown in **Online Table 1**, patients from the EXCELLENT registry represented a higher risk profile, in terms of both clinical and angiographic factors, than those enrolled in the randomised trial. Among a total of 6,524 study patients, 2,404 (36.8%) had diabetes mellitus, while the other 4,120 (63.2%) did not. **Table 1** compares the baseline characteristics of patients treated with EES versus SES according to diabetic status. In terms of demographic variables, patients in the EES group had higher frequencies of hypertension and dyslipidaemia, and a lower frequency of ST-segment elevation myocardial infarction regardless of diabetic status. In patients without diabetes, the EES group had a higher mean age, a lower frequency of previous MI, and a higher frequency of congestive heart failure. Regarding angiographic characteristics, the proportion of previously treated lesions was lower, maximal stent diameter was larger, and total stent length was shorter in the EES group compared to the SES group. Discharge medications were mostly comparable between the two groups.

CLINICAL OUTCOMES

Compared with non-diabetics, those with diabetes mellitus showed poorer clinical outcomes with respect to all composite and individual outcome variables **(Figure 2)**. All pre-specified clinical endpoints, including the primary endpoint, occurred at significantly higher rates in diabetics, except for TVR, TLR, and ST, which were all numerically higher in diabetic patients.

Figure 3 shows the Kaplan-Meier survival curves comparing the incidence of the primary endpoint between EES and SES according to the presence **(Figure 3A)** or absence of diabetes mellitus **(Figure 3B)**. While the absolute rate of TLF was higher in patients with diabetes, both stents showed similar outcomes when compared head-to-head in each subgroup of diabetics and non-diabetics. The interaction between the type of stent and diabetes was not significant (p=0.384). As shown in **Table 2**, there were no significant interactions for any of the secondary endpoints.

Adjusted analyses with IPTW confirmed the results from the crude population **(Table 3)**. There were no significant differences between EES and SES in any of the pre-specified endpoints regardless of diabetic status, while no interaction was found to be significant.

IMPACT OF DIABETES MELLITUS SEVERITY

Among diabetics, 184 (11.9%) and 90 (10.5%) patients had insulin-dependent diabetes in the EES and SES groups, respectively. We found a linear relationship between the severity of diabetes and the occurrence of clinical events **(Figure 4)**. Although p-values were insignificant for ST, and TLR in the SES group, there was a tendency for numerical increment. No interaction between stent type and diabetic severity was present regarding any measured parameters.

The Cox regression model with a forward stepwise method was used to find the independent predictors for TLF. The major contributing factors for TLF were shown to be age, congestive heart failure, chronic renal failure, and clinical diagnosis of acute myocardial infarction, as well as diabetes with a gradient according to its severity. The hazard ratio with the reference of the absence of diabetes was 1.59 (p=0.004) for non-insulin-dependent diabetes, and 2.27 (p=0.004) for insulin-dependent diabetes **(Table 4)**.

Discussion

The major finding of this study is that, in a large PCI population with DES, diabetes mellitus is still a major predictor of adverse events. In addition, the impact of diabetes was consistent regardless of the type of "limus" stent implanted. Moreover, the increase in TLF in diabetic patients was driven not only by repeat revascularisation, but also by hard endpoints including cardiac death and MI. Finally, insulin-dependent diabetes imposed an even higher risk of adverse events than non-insulin-dependent diabetes.

The selection of the optimal treatment strategy for diabetic patients, including medical, interventional, and surgical therapy,

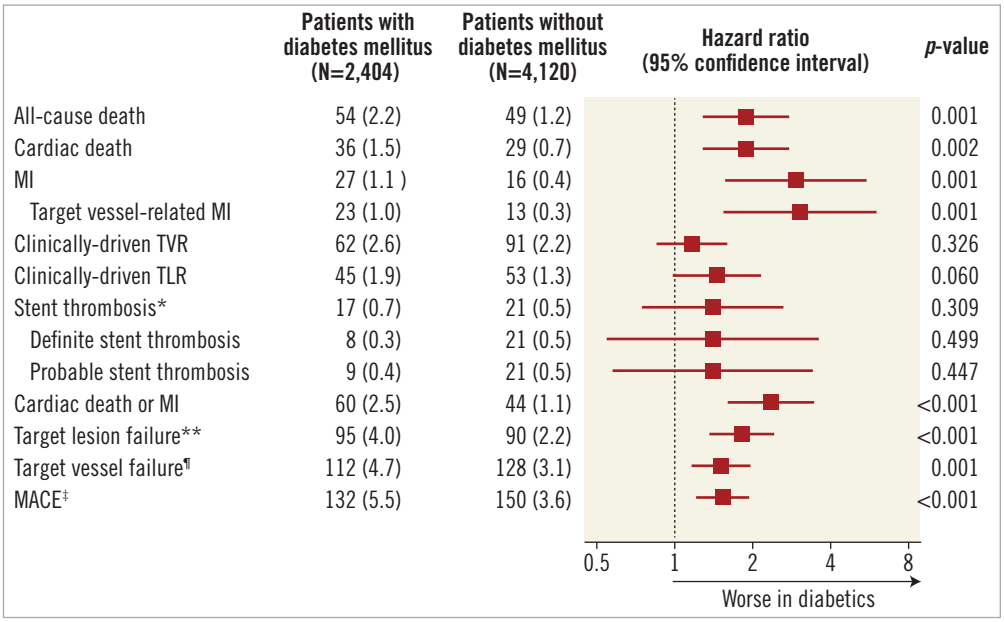

Figure 2. *Clinical outcomes at one year in patients with and without diabetes mellitus. *Stent thrombosis was defined according to the consensus of the Academic Research Consortium. **Target lesion failure was a composite of cardiac death, target vessel-related MI, or clinically-driven TLR. ¶Target vessel failure was a composite of cardiac death, target vessel-related MI, or clinically-driven TVR. ‡MACE was a composite of all-cause death, all-cause MI, or clinically-driven TVR. MACE: major adverse cardiac events; MI: myocardial infarction; TLR: target lesion revascularisation; TVR: target vessel revascularisation*

has been an important issue among cardiovascular physicians. Diabetes is associated with a twofold to fourfold increase in the risk of developing coronary artery disease[20], and patients with diabetes usually have worse outcomes after PCI[1,2]. Although the introduction of DES has potentially reduced the need for repeat revascularisation, diabetic status is still associated with an increased risk for adverse cardiac events in patients undergoing PCI[6-8]. Interestingly, previous studies have demonstrated an interaction between stent type and diabetes in terms of clinical outcomes after PCI: while limus-eluting stents (i.e., EES or SES) show worse

Table 2. Clinical outcomes at 1 year according to diabetic status and stent type.

	Patients with diabetes mellitus (N=2,404)			Patients without diabetes mellitus (N=4,120)			Interaction *p*-value
	EES (N=1,545)	SES (N=859)	*p*-value	EES (N=2,551)	SES (N=1,569)	*p*-value	
All-cause death	37 (2.4)	17 (2.0)	0.491	28 (1.1)	21 (1.3)	0.500	0.318
Cardiac death	22 (1.4)	14 (1.6)	0.710	17 (0.7)	12 (0.8)	0.713	0.986
MI	20 (1.3)	7 (0.8)	0.273	11 (0.4)	5 (0.3)	0.575	0.813
Target vessel-related MI	17 (1.1)	6 (0.7)	0.318	9 (0.4)	4 (0.3)	0.589	0.862
Clinically-driven TVR	41 (2.7)	21 (2.4)	0.676	49 (1.9)	42 (2.7)	0.116	0.219
Clinically-driven TLR	28 (1.8)	17 (2.0)	0.863	28 (1.1)	25 (1.6)	0.179	0.472
Stent thrombosis*	11 (0.7)	6 (0.7)	0.966	10 (0.4)	11 (0.7)	0.176	0.365
Definite stent thrombosis	6 (0.4)	2 (0.2)	0.524	3 (0.1)	7 (0.4)	0.037	0.083
Probable stent thrombosis	5 (0.3)	4 (0.5)	0.588	7 (0.3)	4 (0.3)	0.908	0.637
Cardiac death or MI	40 (2.6)	20 (2.3)	0.664	27 (1.1)	17 (1.1)	0.937	0.741
Target lesion failure**	61 (3.9)	34 (4.0)	0.919	50 (2.0)	40 (2.5)	0.219	0.364
Target vessel failure¶	74 (4.8)	38 (4.4)	0.602	71 (2.8)	57 (3.6)	0.163	0.174
MACE‡	90 (5.8)	42 (4.9)	0.291	84 (3.3)	66 (4.2)	0.138	0.079

EES: everolimus-eluting stent; MACE: major adverse cardiac events; MI: myocardial infarction; SES: sirolimus-eluting stent; TLR, target lesion revascularisation; TVR: target vessel revascularisation; *Stent thrombosis was defined according to the consensus of the Academic Research Consortium; **Target lesion failure was a composite of cardiac death, target vessel-related MI, or clinically-driven TLR; ¶Target vessel failure was a composite of cardiac death, target vessel-related MI, or clinically-driven TVR; ‡MACE was a composite of all-cause death, all-cause MI, or clinically-driven TVR

Table 3. Odds ratios for clinical outcomes with EES versus SES adjusted for inverse probability of treatment weighting.

	Patients with diabetes mellitus (N=2,404)		Patients without diabetes mellitus (N=4,120)		Interaction *p*-value
	OR (95% CI), EES vs. SES	*p*-value	OR (95% CI), EES vs. SES	*p*-value	
All-cause death	1.21 (0.68-2.14)	0.513	0.82 (0.46-1.45)	0.499	0.347
Cardiac death	0.88 (0.45-1.71)	0.699	0.90 (0.43-1.92)	0.794	0.951
MI	1.49 (0.64-3.50)	0.356	1.36 (0.48-3.85)	0.567	0.889
Target vessel-related MI	1.54 (0.61-3.91)	0.359	1.42 (0.45-4.48)	0.553	0.909
Clinically-driven TVR	1.10 (0.66-1.85)	0.712	0.79 (0.52-1.20)	0.266	0.323
Clinically-driven TLR	0.97 (0.54-1.74)	0.928	0.80 (0.46-1.39)	0.436	0.639
Stent thrombosis*	1.20 (0.43-3.31)	0.732	0.62 (0.25-1.56)	0.312	0.352
Definite stent thrombosis	1.70 (0.33-8.82)	0.526	0.27 (0.06-1.13)	0.072	0.097
Probable stent thrombosis	0.93 (0.25-3.45)	0.909	1.35 (0.34-5.28)	0.667	0.697
Cardiac death or MI	1.05 (0.62-1.80)	0.850	1.01 (0.55-1.86)	0.981	0.915
Target lesion failure**	1.00 (0.66-1.52)	0.988	0.84 (0.55-1.29)	0.436	0.587
Target vessel failure¶	1.07 (0.72-1.58)	0.742	0.82 (0.57-1.17)	0.275	0.329
MACE‡	1.17 (0.81-1.70)	0.398	0.82 (0.57-1.14)	0.234	0.155

EES: everolimus-eluting stent; MACE: major adverse cardiac events; MI: myocardial infarction; SES: sirolimus-eluting stent; TLR, target lesion revascularisation; TVR: target vessel revascularisation; *Stent thrombosis was defined according to the consensus of the Academic Research Consortium; **Target lesion failure was a composite of cardiac death, target vessel-related MI, or clinically-driven TLR; ¶Target vessel failure was a composite of cardiac death, target vessel-related MI, or clinically-driven TVR; ‡MACE was a composite of all-cause death, all-cause MI, or clinically-driven TVR

outcomes when implanted to diabetic patients, the performance of paclitaxel-eluting stents remains similar[9-13]. This phenomenon is explained by the different mechanisms of action through which paclitaxel and rapamycin analogues reduce restenosis: whereas paclitaxel interferes with multiple pathways of restenosis, rapamycin analogues work via blocking the PI3K/AKT/mTOR signal axis, a pathway which is already weakened in type II diabetes[21,22].

To the best of our knowledge, this is the largest study to assess the interaction between diabetic status and the use of the two "limus-eluting" stents, EES and SES, which are currently the most widely used among DES. Kim et al showed in the ESSENCE-DIABETES randomised trial that, among diabetic patients, EES was non-inferior to SES in terms of angiographic outcomes[23]. A substudy of the SORT OUT IV trial showed no significant differences in clinical outcomes between EES and SES in diabetic or non-diabetic patients[24]. Kufner et al also showed comparable outcomes between EES and SES in patients with diabetes enrolled in the ISAR-TEST-4 trial[25]. Our study has the merit that it reflects

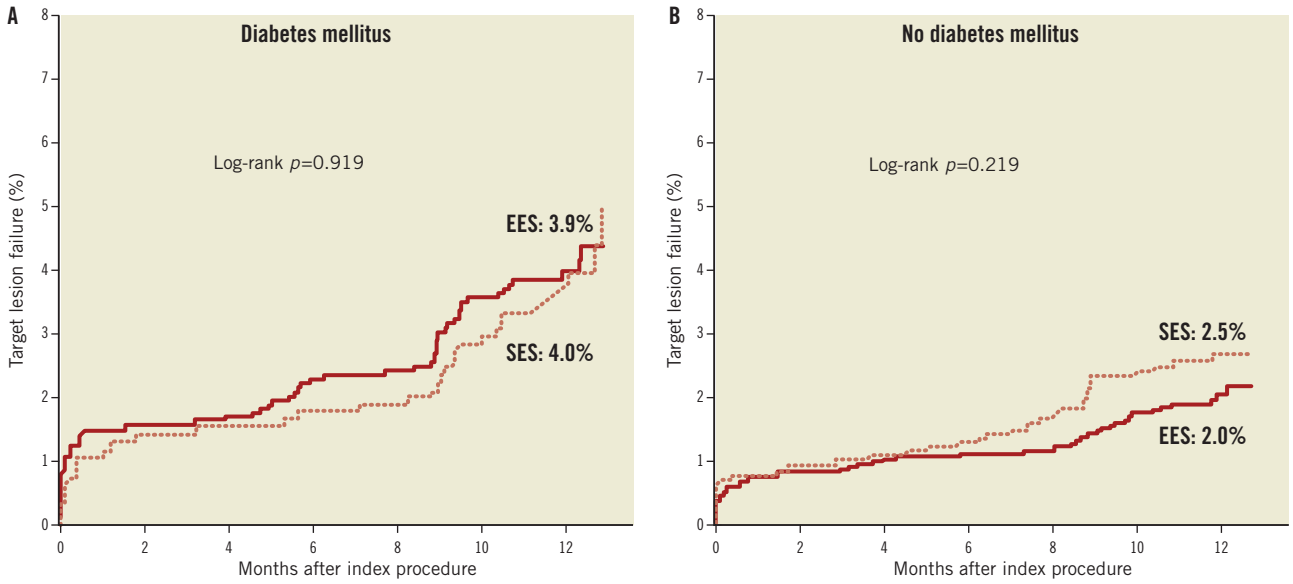

Figure 3. *Kaplan-Meier survival curves of target lesion failure in patients treated with everolimus-eluting stents (EES) versus sirolimus-eluting stents (SES) according to diabetic status. EES: everolimus-eluting stent; SES: sirolimus-eluting stent*

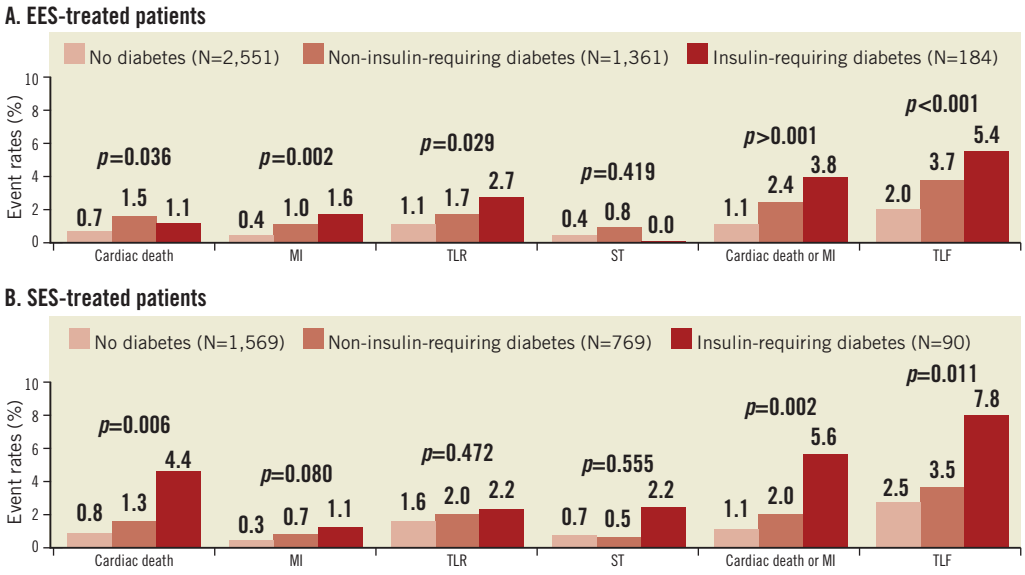

Figure 4. *Event rates in patients without diabetes, with diabetes not requiring insulin, and with diabetes requiring insulin. MI: myocardial infarction; ST: stent thrombosis; TLF: target lesion failure; TLR: target lesion revascularisation; TVR: target vessel revascularisation*

Table 4. Independent predictors for target lesion failure at 1 year (Cox proportional hazards model).

	Hazard ratio	95% Confidence interval	*p*-value
Chronic renal failure	2.74	1.57-4.77	<0.001
Congestive heart failure	2.34	1.21-4.51	0.011
Acute myocardial infarction	1.78	1.29-2.45	<0.001
Age - per 10 years	1.43	1.23-1.66	<0.001
Diabetes mellitus			0.001
Non-insulin-dependent	1.59	1.16-2.18	0.004
Insulin-dependent	2.27	1.30-3.96	0.004

Target lesion failure was defined as a composite of cardiac death, target vessel-related MI, or clinically-driven TLR.

a broader study population, as we pooled patients from a randomised trial with strict inclusion criteria and a "real-world" robust registry. These results dispel those concerns that the issue of attenuated efficacy may be a problem specific to EES.

It is notable that in this study the risk of device-specific clinical events (i.e., TLR, TVR, and ST) did not differ significantly between diabetics and non-diabetics. Similarly, a recent pooled analysis of RESOLUTE programmes also showed no significant differences between diabetics and non-diabetics as well as insulin-treated and non-insulin-taking patients[26]. These results should be interpreted with caution, because the occurrence of those events was still numerically high. Although a statistical significance has disappeared due to the low statistical power provoked by the improved performance of recently developed DES, the relative risk still remains the same: risk ratio of TLR and TVR between 1.2-1.5, and that of ST around 1.5[10,26].

Despite recent advances in interventional devices, this study showed that diabetes mellitus still remains a hurdle to be overcome when a patient with coronary artery disease is treated with PCI. Further improvement in device technology may be able to tackle this issue. However, one of the major findings of this study is that the increase in the primary endpoint originated more from cardiac death and MI rather than from device-specific endpoints. Thus, it can be speculated that there is little room for device innovation. The remaining question may be whether more intensive glycaemic control would improve outcomes after PCI in diabetic patients. This needs to be investigated in future trials.

Limitations

This study has several limitations. First, as we pooled data from a randomised trial and an observational registry, the analysed cohort was heterogeneous. Although this is the largest study testing the relative efficacy of EES versus SES stratified by the status of diabetes mellitus, the results should be considered hypothesis-generating at best. Second, clinical follow-up was restricted to one year. Late or very late stent thrombosis is the major concern regarding the safety of DES, and this could not be captured in this study. Third, patients with diabetes mellitus show a high frequency of silent myocardial ischaemia. As this study did not mandate angiographic follow-up, recurrent ischaemia could have been overlooked. Fourth, as event rates were low in this study, we cannot exclude that the study was underpowered.

Conclusions

In this study, we found that patients with diabetes mellitus were at increased risk of adverse cardiac events after PCI when treated with EES or SES. Furthermore, the increased risk in diabetics compared

to non-diabetics had no significant interaction with whether the patient was treated with EES or SES.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Online data supplement

Online Table 1. Baseline characteristics.

Online data supplement

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	RCT (N=1,406)	Registry (N=5,118)	*p*-value
Demographic & clinical variables			
Age - years	62.7±10.0	63.3±10.8	0.090
Male	905 (64.4)	3,479 (68.0)	0.011
Body mass index - kg/m^2	25.0±3.1	24.7±3.5	0.005
Hypertension	1,031 (73.3)	3,162 (61.8)	<0.001
Dyslipidaemia	1,064 (75.7)	3,310 (64.7)	<0.001
Current smoking	372 (26.5)	1,540 (30.1)	0.008
Chronic renal failure	15 (1.1)	159 (3.1)	<0.001
Peripheral artery disease	19 (1.4)	74 (1.4)	0.791
Previous cerebrovascular disease	93 (6.6)	371 (7.2)	0.412
Previous myocardial infarction	72 (5.1)	426 (8.3)	<0.001
Congestive heart failure	9 (0.6)	94 (1.8)	0.001
Family history of coronary artery disease	123 (8.7)	273 (5.3)	<0.001
Left ventricular ejection fraction - %	61.3±9.5	59.3±11.6	<0.001
Clinical indication			<0.001
Silent ischaemia	55 (3.9)	152 (3.0)	
Stable angina	632 (45.0)	1,757 (34.8)	
Unstable angina	582 (41.4)	1,803 (35.7)	
Non-ST-elevation myocardial infarction	95 (6.8)	570 (11.3)	
ST-elevation myocardial infarction	42 (3.0)	765 (15.2)	
Angiographic variables			
Extent of disease			0.050
Single-vessel disease	680 (48.4)	2,346 (46.0)	
Two-vessel disease	446 (31.7)	1,586 (31.1)	
Three-vessel disease	280 (19.9)	1,170 (22.9)	
Number of lesions	1.3±0.6	1.5±0.7	<0.001
Left main coronary artery lesion	0 (0.0)	304 (5.9)	<0.001
Thrombus	124 (8.8)	479 (9.4)	0.536
Previously treated lesions	0 (0.0)	475 (9.3)	<0.001
Bifurcation lesion	392 (27.9)	679 (13.3)	<0.001
Number of stents per patient	1.2±0.5	1.6±0.9	<0.001
Maximal stent diameter - mm	3.1±0.4	3.2±0.4	0.082
Total stent length - mm	28.3±13.6	38.2±25.0	<0.001
Discharge medications			
Aspirin	1,384 (99.2)	5,001 (97.7)	<0.001
Clopidogrel	1,386 (99.4)	4,979 (97.3)	<0.001
β-blockers	534 (38.3)	1,925 (37.6)	0.649
ACE inhibitors	458 (32.8)	1,949 (38.1)	<0.001
Angiotensin receptor antagonist	467 (33.5)	1,599 (31.2)	0.112
Statins	1,160 (83.2)	4,278 (83.6)	0.699
Calcium channel blockers	475 (34.1)	1,426 (27.9)	<0.001
Oral hypoglycaemic agents	323 (23.2)	1,081 (21.1)	0.102
Insulin	45 (3.2)	190 (3.7)	0.388

RCT: randomised controlled trial