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Clinical research

Sirolimus-eluting stents inhibit neointimal hyperplasia in diabetic patients

Insights from the RAVEL Trial

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Patients with diabetes mellitus have less favourable outcomes after percutaneous coronary intervention (PCI) than non-diabetics. We performed a subgroup analysis of the multicentre RAVEL trial to examine the impact of the sirolimus-eluting stent (SES) on outcomes in diabetic patients. The RAVEL study randomized 238 patients to treatment with either sirolimus-eluting or bare metal stents. Forty-four patients were diabetic; 19 received sirolimus-eluting stents and 25 were treated with bare metal stents. The differences in outcomes between diabetic and non-diabetic patients treated with SES (n=101) were also assessed. Follow-up angiography was performed at 6 months. Major adverse cardiac events (MACE) defined as death, myocardial infarction (MI), or target lesion revascularization (TLR) were analysed at 12-month follow-up. Six-month in-stent late lumen loss was significantly lower for the diabetic SES than the bare stent group (0.07±0.2 vs 0.82±0.5 mm; P<0.001) and similar to that in non-diabetics treated with SES (−0.03±0.27 mm). There was zero restenosis in the SES groups (diabetic and non-diabetic) compared to a 42% rate in the diabetic population assigned to bare metal stents (P=0.001). After 12 months, there was one non-Q-wave MI and one non-cardiac death in the diabetic SES group, while 12 patients in the bare metal stent group had MACE (one death, two MI, nine TLR) (P=0.01) — an event-free survival rate of 90% vs 52%, respectively (P<0.01). There were no TLRs in both SES groups compared to 36% rate in the diabetic bare metal stent group (P=0.007).

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Conclusion Diabetics treated with SES were associated with a virtual abolition of neointimal proliferation and low event rates at long-term follow-up.

Introduction

Diabetes mellitus has been found to be an important risk factor for poor outcome after percutaneous transluminal coronary angioplasty.[1–3] Although coronary stents improve acute results and decrease restenosis rates compared to balloon angioplasty, diabetes remains a key independent predictor of in-stent restenosis.[4–6] Sirolimus-eluting stents have been shown to be a safe and effective therapy to inhibit neointimal formation, thereby significantly reducing restenosis.[7–9] The purpose of this study was to evaluate the impact of sirolimus-eluting stents (SES) on the treatment of diabetic patients with coronary artery disease. We evaluated the clinical and angiographic outcomes of diabetic patients enrolled in the multicentre RAVEL trial and compared these results with the outcomes of both the diabetic population treated with bare metal stents and non-diabetic patients treated with SES.

Methods

Trial design

A detailed description of the RAVEL (randomized study with the sirolimus-coated Bx velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions) protocol has been reported previously.[9] Patients were eligible for the study if they had a single primary target lesion in a native coronary artery 2.5 to 3.5 mm in diameter by visual assessment that could be covered by an 18-mm stent.

Study population

Between August 2000 and August 2001, 238 patients were randomized to receive either the sirolimus-eluting Bx VELOCITY™ stent or the standard stent implantation. In this trial 44 patients (19%) were diabetics: 25 patients were randomized to receive bare metal stents (n=25, diabetic-BS group) and 19 patients were treated with SES (diabetic-SES group). There were 101 non-diabetic patients treated with sirolimus-eluting stents (non-diabetic-SES group) in the RAVEL study.

Diabetic patients were identified by patient-reported history, and divided according to their treatment regimen: insulin-dependent and non-insulin dependent diabetes.

The sirolimus-eluting stent

The balloon-expandable stent (Bx VELOCITY™, Cordis, Johnson & Johnson) was loaded with a fixed amount of sirolimus per unit of metal surface area (140 μg of sirolimus per square centimetre). A layer of drug-free polymer was applied on top of the drug-polymer matrix as a diffusion barrier to prolong the release of the drug. The stent was designed to release approximately 80% of the drug within 30 days after implantation.

Procedural characteristics

Lesions were treated with the use of standard interventional techniques. Direct stenting was not allowed. After successful predilatation, patients were randomly assigned to receive a standard bare metal stent or a SES mounted on a rapid-exchange delivery system. The SESs were indistinguishable from bare metal stents. The anti-thrombotic regimen included aspirin at a dose of at least 100 mg per day started 12 h before the procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administrated 48 h before the procedure, followed by 75 mg daily for 8 weeks. Alternatively, ticlopidine, at a dose of 250 mg twice daily, was given.

Follow-up evaluation

Repeat angiography was scheduled at 6-month follow-up and quantitative analyses of all angiographic data were performed off-line by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands). Restenosis was defined as stenosis of 50% or more of the luminal diameter. Late luminal loss was defined as the difference between the minimal luminal diameter immediately after the procedure and the diameter at 6 months. The target lesion was defined as the stented segment plus 5 mm segments proximal and distal to the stented segment. At the 6-month visit, intravascular ultrasound examination was performed by six centres in 95 patients. In the subgroup of diabetics, intravascular ultrasound analysis (IVUS) was performed in 10 patients assigned to sirolimus-eluting stents and 12 assigned to the standard stents. Twelve month clinical events were collected in all patients.

IVUS analysis

Intravascular ultrasound images images were acquired by motorized pullback at a constant speed of 0.5 mm/s. Quantitative angiographic and volumetric IVUS analyses were performed by independent core laboratories (Brigham and Women's Hospital, Boston, Mass, and Cardialysis BV, Rotterdam, The Netherlands, respectively). Validation of volumetric IVUS quantification has been described elsewhere. Intimal hyperplasia volume was calculated as stent volume minus luminal volume. Percent intimal hyperplasia was defined as intimal hyperplasia volume divided by stent volume.

Statistical analysis

Continuous variables were expressed as means ± SD and were compared using the unpaired Student's t-test. The Fisher's exact test was used for categorical variables. Binary outcome variables are reported as frequencies and percentages and were compared in terms of relative risk with 95% confidence intervals calculated by the formula of Greenland and Robins.[10] Target

Table 1 Baseline characteristics[a]

Variables	SES DM (*n*=19)	Bare DM (*n*=25)	SES non-DM (*n*=101)	Bare non-DM (*n*=93)
Age (years)	64.2±9.3	63.6±8.4	61.3±10.9	58.6±10.3
Male gender	68.4% (13)	80.0% (20)	70.3% (71)	81.7% (76)
Hypercholesterolaemia	42.1% (8)	48.0% (12)	49.5% (50)	56.5% (52)
Hypertension	89.5% (17)	72.0% (18)	43.6% (44)	40.9% (38)
Previous MI	36.8% (7)	44.0% (11)	37.6% (38)	31.2% (29)
Previous CABG	0.0%	0.0%	2.0% (2)	2.2% (2)
Previous PTCA	26.3% (5)	24.0% (6)	17.8% (18)	15.1% (14)
Smoking history				
Previous	36.8% (7)	48.0% (12)	43.6% (44)	29.0% (27)
Current	21.1% (4)	8.0% (2)	27.7% (28)	39.8% (37)
Unstable angina				
Braunwald I	5.3% (1)	0.0%	15.2% (15)	11.8% (11)
Braunwald II	15.8% (3)	29.2% (7)	22.2% (22)	23.7% (22)
Braunwald III	10.5% (2)	16.7% (4)	14.1% (14)	18.3% (17)
Stable angina				
CCS I	5.3% (1)	12.5% (3)	4.0% (4)	4.3% (4)
CCS II	26.3% (5)	16.7% (4)	24.2% (24)	18.3% (17)
CCS III	15.8% (3)	12.5% (3)	10.1% (10)	12.9% (12)
CCS IV	0.0%	0.0% (0)	1.0% (1)	0.0%
Silent ischaemia	21.1% (4)	12.5% (3)	9.1% (9)	10.8% (10)
Number of diseased arteries				
Single	68.4% (13)	64.0% (16)	71.3% (72)	72.0% (67)
Double	31.6% (6)	24.0% (6)	20.8% (21)	23.7% (22)
Triple	0.0%	12.0% (3)	7.9% (8)	4.3% (4)

[a]Numbers are percent or mean±1 standard deviation.
CCS: Canadian Cardiovascular Society Classification; MI: myocardial infarction; CABG: coronary artery bypass graft; PTCA: percutaneous transluminal coronary angioplasty; SES: indicates sirolimus-eluting stents; DM: indicates diabetics; non-DM: non-diabetics.

Table 2 Baseline angiographic characteristics of the four subgroups

Variables	SES DM (*n*=19)	Bare DM (*n*=25)	SES non-DM (*n*=101)	Bare non-DM (*n*=93)
Lesion location				
RCA	42.1% (8)	24.0% (6)	23.8% (24)	27.2% (25)
LM	0.0% (0)	0.0%	0.0%	0.0%
LAD	47.4% (9)	56.0% (14)	49.5% (50)	50.0% (46)
LCX	10.5% (2)	20.0% (5)	26.7% (27)	22.8% (21)
Length				
<10 mm	78.9% (15)	54.2% (13)	78.4% (76)	80.0% (72)
10–20 mm	21.1% (4)	45.8% (11)	21.6% (21)	20.0% (18)
>20 mm	0.0%	0.0%	0.0%	0.0%
Ostial lesion	0.0%	0.0%	0.0%	0.0%
Calcification: moderate to heavy	26.3% (5)	28.0% (7)	22.7% (22)	23.3% (21)
Thrombus present	5.3% (1)	0.0%	4.1% (4)	2.2% (2)
Lesion classification[a]				
Type A	0.0% (0)	4.0% (1)	8.9% (9)	4.3% (4)
Type B1	42.1% (8)	28.0% (7)	37.6% (38)	37.0% (34)
Type B2	57.9% (11)	68.0% (17)	53.5% (54)	58.7% (54)
Type C	0.0% (0)	0.0%	0.0%	0.0%

[a]American College of Cardiology/American Heart Association Lesion Class.

lesion revascularization and the composite of major adverse events during follow-up were analysed by the Kaplan–Meier method. Differences between the event-free survival curves for the two groups were compared with the use of the Wilcoxon and long-rank tests. All statistical tests were two-tailed and a *P*-value <0.05 was considered significant.

Results

Baseline demographics and angiographic characteristics were similar between the two diabetic sub-groups (Tables 1 and 2). Each diabetic sub-group had five patients with insulin-dependent diabetics.

Table 3 Results of sub-segmental quantitative angiographic analysis

	Proximal edge			Stented segment			Distal edge		
	SES DM (*n*=19)	Bare DM (*n*=25)	*P* value	SES DM (*n*=19)	Bare DM (*n*=25)	*P* value	SES DM (*n*=19)	Bare DM (*n*=25)	*P* value
Baseline									
MLD	2.14±0.47	2.13±0.58	0.92	0.99±0.24	0.93±0.33	0.49	1.88±0.44	1.94±0.60	0.71
DS (%)	15.06±6.64	16.76±8.38	0.47	60±9	63±10	0.29	16.87±10.25	15.38±7.99	0.59
Post									
MLD	2.34±0.40	2.39±0.45	0.70	2.37±0.43	2.36±0.45	0.93	2.00±0.47	2.12±0.49	0.45
DS (%)	12.38±6.96	12.97±4.08	0.75	13±6	14±9	0.66	14.95±6.52	11.82±4.41	0.06
Follow-up									
MLD	2.22±0.49	2.10±0.67	0.51	2.31±0.40	1.56±0.64	<0.001	2.08±0.55	2.06±0.53	0.92
DS (%)	12.47±4.14	17.70±9.04	0.018	16±5	38±21	<0.001	13.19±7.16	13.30±4.50	0.96
Late loss[a]	0.08±0.31	0.31±0.49	0.10	0.07±0.20	0.82±0.53	<0.001	−0.06±0.26	0.07±0.29	0.17
Late loss index[b]	2.20±3.42	−1.23±11.26	0.19	0.04±0.15	0.57±0.37	<0.001	−8.57±22.19	1.09±5.95	0.11

[a]Late loss was defined as the difference between the minimal luminal diameter immediately after placement of the stent and the minimal luminal diameter at six months.
[b]Late loss index was defined as late loss divided by the reference diameter.

Table 4 Intravascular ultrasound volumetric analysis

	SES DM (*n*=19)	Bare DM (*n*=25)	*P*
EEM volume (mm^3)	297.9±70.6	277.0±64.2	0.64
Stent volume (mm^3)	121.9±33.8	123.8±29.2	0.90
Lumen volume (mm^3)	121.0±33.7	88.9±45.5	0.02
PM volume (mm^3)	169.6±48.5	189.1±52.3	0.03
Neo-intimal volume (mm^3)	0.90±1.2	34.9±28.9	0.01
Volume obstruction in-stent (%)	0.82±1.4	30.2±22.9	0.008

Procedural characteristics

Platelet glycoprotein IIb/IIIa inhibitors was administrated in only one patient from the sirolimus diabetic cohort was, whereas no use was reported in the diabetic control group. A total of 12/101 patients (11.9%) and 10/92 patients (10.9%) use GPIIb/IIIa in the sirolimus and bare non-diabetics groups, respectively. All patients from the two diabetic subgroups underwent successful stent implantation, whereas the sirolimus and bare non-diabetics groups had a success rate of 96 and 92%, respectively. Both diabetics' sub-groups utilized only one stent per patient, whereas 103 (mean 1.0±0.3) and 94 (1.1±0.3) stents were implanted in the SES and bare stent non-diabetic groups, respectively. Mean stent diameter used was similar between all groups: SES diabetics (3.03±0.31 mm), bare stent diabetics (3.12±0.26 mm), SES non-diabetics (3.07±0.35 mm) and bare stent non-diabetics (3.1±0.30 mm).

Quantitative angiographic analysis

Quantitative angiography revealed similar baseline and post procedure measurements (Table 3) between the two diabetic subgroups. However, at 6-months follow-up, late lumen loss was significantly lower for the sirolimus group (0.07±0.20 vs 0.82±0.53 mm; *P*<0.001), resulting in a significantly lower mean percent diameter stenosis (16±5% vs 38±21%; *P*<0.001) and binary restenosis rate (0 vs 42%; *P*<0.001) in the diabetic-SES group compared to diabetic-BS (Table 3). It is worth noting that the late lumen loss at follow-up was similar in the diabetic-SES and non-diabetic-SES groups (0.07±0.20 vs −0.03±0.27 mm, *P*=0.12, respectively).

IVUS analysis

Quantitative volumetric IVUS analysis, albeit in a small group of patients, confirmed the marked inhibition of tissue proliferation with sirolimus as observed with quantitative angiography. The neointimal hyperplasia volumes were 0.9±1.2 vs 34.9±28.9 mm^3 (*P*=0.01) and percent in-stent volume obstruction 0.82±1.38% vs 30.2±22.9% (*P*=0.008), respectively, in the diabetic-SES and diabetic-BS groups (Table 4). Intravascular ultrasound data from diabetic-SES group compared favourably with non-diabetic-SES patients in whom neointimal hyperplasia volume and percent volume obstruction were 1.6±4.60mm^3 and 1.14±2.68%, respectively.

Table 5 Major cardiac events up to 1-year follow-up

	SES DM (*n*=19)	Bare DM (*n*=25)	*P*
Death	1 (5.3%)	1 (4%)	1.0
Non-fatal MI	1 (5.3%)	2 (8%)	1.0
Q-wave MI	1(4%)	0 (0%)	1.0
Non Q-wave MI	1 (5.3%)	2 (8%)	1.0
Late thrombosis	0 (0%)	0 (0%)	
Target lesion CABG	0 (0%)	1 (4%)	1.0
Target lesion re-PTCA	0 (0%)	8 (32%)	0.007
MACE (death, MI, TLR)	2 (10.5%)	12 (48%)	0.01

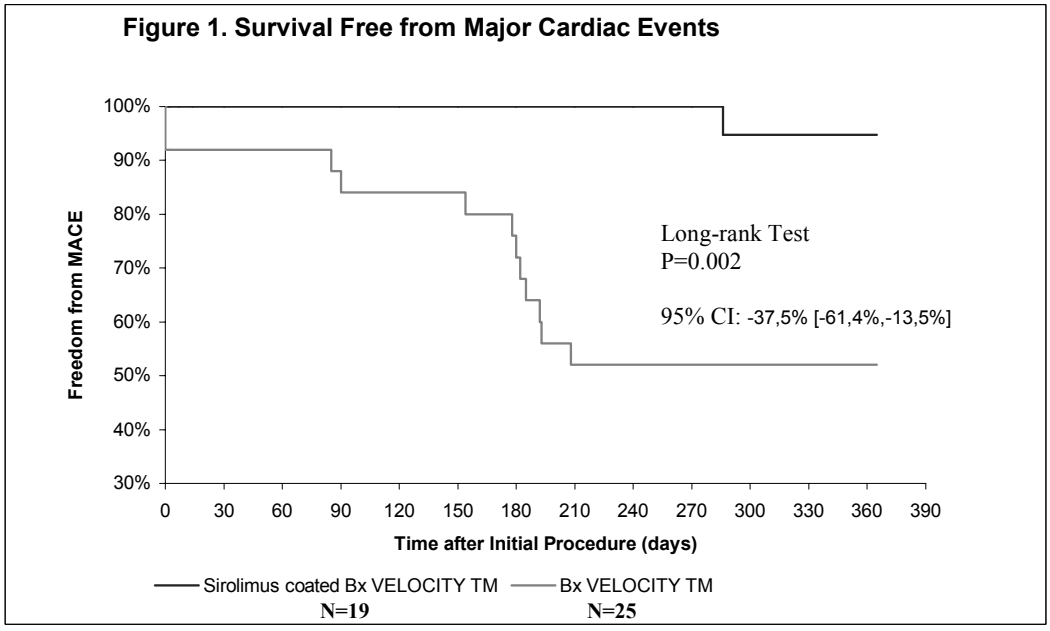
One-year clinical outcome

Patients assigned to bare stents had a higher incidence of combined major adverse cardiac events (MACE) as compared to those randomized to SES (Table 5). In the diabetic-SES group there was one non-cardiac death and one non-Q-wave myocardial infarction (MI). Conversely, 12 patients (48%) randomized to standard stents presented with major cardiac events (Table 5, *P*=0.01). Diabetic patients treated with SES as compared to a bare stent had ahad a significantly higher 1-year event-free survival rate (Fig. 1) mainly due to a lower incidence of repeat revascularization (Table 5).

Discussion

This study, which is a sub-analysis of the RAVEL trial, indicates that sirolimus-eluting stents provides superior long-term results compared to bare metal stents for the treatment of non-complex lesions in diabetic patients. Sirolumus-eluting stents appear to largely neutralize the exaggerated in-stent neointimal proliferation commonly associated with diabetes. Six-month angiographic and IVUS outcomes were similar between diabetic and non-diabetic patients treated with SES. There were zero restenosis by angiography or target lesion revascularizations in patients treated with SES, regardless of their diabetic status.

Conventional stents have improved the outcomes of diabetic patients compared to balloon angioplasty.[4–6] However, diabetics still represent a high-risk group for restenosis and unfavourable clinical outcome after percutaneous coronary interventions because of exaggerated neointimal proliferation.[11] In the TARGET trial,[12] which compared abciximad versus tirofiban following elective stent implantation, 6-month target vessel failure and major adverse cardiac event rates in the diabetic population (*n*=1117) were 14.3 and 16%, respectively.



Interval ending day	0	2	7	14	30	60	90	120	150	180	210	240	270	300	330	365
# Events Bx Velocity	0	2	0	0	0	0	2	0	0	3	5	0	0	0	0	0
# Events Sirolimus	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0

CI: indicates confidence intervals

Fig. 1 Kaplan–Meier event-free survival curves for major cardiac events in diabetic patients assigned to sirolimus-eluting stents versus bare stents (*P*=0.01).

Many of these patients requiring repeat revascularization develop a rather diffuse type of in-stent restenosis and, particularly those with multivessel disease, were likely to undergo, are referred to coronary bypass graft surgery (CABG).[3,13] The high rates of restenosis (42%) and clinical events observed in diabetic patients treated with conventional bare metal stents in the present study further highlight the impact of diabetes mellitus on clinical outcomes after conventional stenting. By contrast, the finding of zero restenosis, minimal neointimal proliferation and no need for repeat revascularization in the diabetic population speaks to the potent antiproliferative and anti-inflammatory effects of sirolimus.[14]

The small cohort of patients with diabetes enrolled in the RAVEL trial precludes a definitive scientific conclusion about the value of SES in these patients. Furthermore, the less complex demographics and lesion characteristics included in RAVEL might explain the differences found in the more 'real-world' SIRIUS trial (n=1100). In the SIRIUS trial,[15] longer lesions (14.4 vs 9.6 mm in RAVEL, P=0.001) were included, however, vessel size was bigger than in RAVEL (2.80 vs 2.6 mm, P=0.001). In the diabetic SES subgroup (n=131) lower restenosis (17.6% vs 50.5%, P<0.001) and target vessel revascularization (6.9 vs 22.3%, P<0.001) rates were observed when compared to non-SES subgroup (n=148). Nevertheless, the dramatic reduction in restenosis and need for revascularization seen with the RAVEL SES group, and the fact that angiographic late loss and percent volume obstruction by IVUS (the most direct measures of tissue proliferation) the SES group were similar in diabetics and non-diabetics, suggests that SES implantation may partially or totally neutralize the impact of diabetes mellitus on restenosis.

While prevention of restenosis is clearly a major therapeutic objective, diabetics remain at high risk for late vascular events in other vascular beds and require a multidisciplinary therapeutic approach.[16] The present study findings warrant confirmation by large randomized investigations to determine whether the need for repeat intervention with SES is consistently better than with bare metal stents, and whether the long-term clinical outcomes of diabetics treated with SES are comparable to those treated with coronary artery bypass surgery.

Limitations

A diabetic subgroup was not pre-specified in the original focus of the RAVEL trial. Moreover, the small size and selective nature of the study population are inherent limitations of this sub-analysis. However, these data from the first prospective, randomized trial comparing bare stents and SES will provide an important frame of reference for future clinical trials of diabetics.

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