Long-term clinical benefit of sirolimus-eluting stent implantation in diabetic patients with de novo coronary stenoses: long-term results of the DIABETES trial

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Aims Sirolimus stent implantation has been demonstrated to be safe and effective in diabetics; however, the long-term outcomes in this high-risk population remain unknown. The aim of this study was to determine the long-term safety and efficacy of the sirolimus-eluting stent (SES) when compared with the bare metal stent (BMS) in patients included in the DIABETES (DIABETes and sirolimus Eluting Stent) trial.

Methods and results The prospective multicentre DIABETES trial randomized 160 diabetic patients with one or more significant coronary stenoses in one, two, or three vessels to either SES or BMS implantation. One-year dual antiplatelet therapy (aspirin plus clopidogrel) was routinely prescribed. Clinical follow-up was scheduled at 1, 9, 12, and 13 months and 2 years. Baseline clinical and angiographic characteristics were comparable between groups. At 2 years, the rate of target lesion revascularization was significantly lower in the SES group compared with the BMS group (7.7 vs. 35.0%, \( P < 0.001 \)). However, the total revascularization rate at 2 years increased in both groups due to progression of atherosclerosis in coronary segments remote from the target lesion (rate of atherosclerosis progression: 7.7% in SES group vs. 10% in BMS group; \( P = 0.7 \)). During dual antiplatelet treatment (1 year), there was no stent thrombosis in the SES group, whereas two patients presented it in the BMS group. However, after clopidogrel withdrawal, three patients allocated to the SES group presented stent thromboses vs. none in the BMS group.

Conclusion SES implantation in diabetic patients remains effective at 2-year follow-up. However, clinical efficacy appeared to be reduced by the occurrence of stent thrombosis between 1 and 2 years.

KEYWORDS
Sirolimus-eluting stent; Restenosis; Diabetes mellitus; Stent thrombosis; Target lesion revascularization; Trial

Introduction

Percutaneous coronary interventions in patients with diabetes mellitus have been flawed by elevated rates of restenosis and progression of the atherosclerotic disease.¹–⁴ Drug-eluting stents have a markedly reduced restenosis rate in the general population.⁵–⁸ Furthermore, retrospective subgroup analyses of randomized clinical trials have also demonstrated a reduction in restenosis rates in diabetic patients.⁹,¹⁰ Nevertheless, the presence of diabetes mellitus still remains an independent predictor of target lesion revascularization (TLR).⁹ Besides, a more aggressive and diffuse pattern of atherosclerotic disease¹¹ and a prothrombotic state,¹² which characterize diabetics, constitute additional determinants of unfavourable long-term outcomes in these patients.

The DIABETES (DIABETes and sirolimus Eluting Stent) trial was the first multicentre randomized trial aimed to prospectively assess the efficacy of sirolimus-eluting stent (SES) to prevent restenosis in diabetic patients with de novo coronary stenoses.¹³ At 9-month follow-up, patients treated with SES presented a significant reduction in late lumen loss, binary restenosis, and TLR compared with those treated with bare-metal stent (BMS).¹³

We report the 2-year clinical results of the patients included in the DIABETES trial. For the purpose of the study, we specifically addressed the long-term effects of SES implantation, as well as the impact of atherosclerotic disease progression and the risk of stent thrombosis associated with clopidogrel withdrawal in this population.
Methods

Study design and eligibility

The design, exclusion and inclusion criteria, and the data collection of the DIABETES trial have been previously described. In brief, patients were eligible for the study if they were either non-insulin or insulin-dependent diabetics according to the World Health Organization Report. All patients were on pharmacological treatment (insulin or hypoglycaemic agents) for at least 1 month. Patients eligible for the study were randomized to treatment with SES (Cypher, Cordis, Johnson & Johnson) or BMS (Bx Velocity/Sonic, Cordis, Johnson & Johnson) in a 1:1 ratio. The randomization was centralized and stratified by diabetes treatment status: insulin-dependent or non-insulin-dependent. The use of abximab was recommended per protocol, and dual antiplatelet therapy (aspirin plus clopidogrel) was routinely prescribed for 1 year in both arms. The study was approved by the Institutional Review Board of each participating centre and all patients signed a written informed consent.

Data collection, follow-up, and core laboratory analyses

After discharge, clinical follow-up was obtained at 1, 9, 12, 13 (1 month after clopidogrel withdrawal), and 24 months. Angiographic follow-up was performed at 9 months. A centralized coordinating centre (San Carlos University Hospital, Madrid, Spain) was responsible for all the data collection from all participating sites. All clinical endpoints were adjudicated by an independent clinical-events committee unaware of the treatment-group assignment.

Study endpoints and definitions

This study described the 2-year follow-up of diabetes trial (secondary endpoint) focusing on major adverse cardiac events (MACE) defined as the composite of cardiac death, myocardial infarction (MI), TLR (in-segment zone), and stent thrombosis at 1, 9, 12, 24 months. The angiographic results at 9 months (primary endpoint) and intravascular ultrasound (IVUS) data were previously published.

Clinically driven TLR was defined as repeat revascularization owing to stenosis of at least 50% of the luminal diameter (in-segment zone) and a functional study indicating ischaemia or if there was stenosis of at least 70% in conjunction with recurrent symptoms alone.

MI was defined as the occurrence of prolonged typical chest pain and/or either the development of pathological Q-waves lasting at least 0.04 s in at least two contiguous leads with an elevated creatine kinase MB fraction level or, in the absence of pathological Q-waves, an elevation in creatine kinase levels to more than twice the upper limit of normal with an elevated creatine kinase MB level.

Revascularization due to progression of atherosclerosis was defined as the need for revascularization secondary to the appearance of any new significant coronary stenoses, present only in the follow-up angiogram, accompanied by symptoms or evidence of ischemia.

Total revascularization included the need for new revascularization due to restenosis and/or atherosclerosis progression.

Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel. In the absence of angiographic confirmation, either acute MI in the distribution of the treated vessel or sudden death was considered as stent thrombosis.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and categorical variables as percentages. Comparisons between groups were performed by Student’s t-test for quantitative variables following evaluation of normal distribution (Kolmogorov-Smirnov) test. Categorical variables were compared by means of Fisher’s exact test. The rate of survival free from TLR and revascularization of any cause during 2-year follow-up period was analysed with the use of the Kaplan–Meier analyses, and the difference between rates was assessed by the log-rank test. Stratified analyses were performed to assess the clinical efficacy in the following pre-specified variables: diabetes status, gender, left anterior descending artery, use of glycoprotein IIb/IIa inhibitors, chronic total occlusion, lesions length, and stent size. To identify factors that might be related to TLR, backward COX-regression models were used including those variables with a P < 0.1 or those clinically relevant. The assumption of the proportional hazard was verified.

The variables finally included in the model were diabetes status (insulin or non insulin treated), peripheral vasculopathy, creatinine level, the number of disease vessels, baseline and post-procedure minimal luminal diameter at target site, vessel size, stent type and stent length. In addition, to take into account the intra-individual variability, the analysis of lesions (repeated assessments) was adjusted by means of a generalized estimating equations model. All statistical analyses were performed with the use of SPSS (version 12.0) or STATA (version 9.0) software, and all reported P-values were two-sided. We assumed significance at the 5% level (P < 0.05).

Results

Baseline characteristics

Between February 2003 and November 2003, 160 diabetic patients were randomized to treatment with SES (n = 80) or BMS (n = 80). Thirty-three percent of the patients were insulin-dependent. Overall, 111 lesions were treated with SES and 110 with BMS implantation. There was not relevant clinical evidence for a difference between groups in the baseline characteristics (Table 1).

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>SES group (n = 80)</th>
<th>BMS group (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.9 ± 9</td>
<td>67.2 ± 10</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>30 (37.5)</td>
<td>30 (37.5)</td>
</tr>
<tr>
<td>Insulin-treated, n (%)</td>
<td>26 (32.5)</td>
<td>27 (33.8)</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>49 (61.3)</td>
<td>49 (61.3)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>53 (66.3)</td>
<td>53 (66.3)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>36 (45.0)</td>
<td>40 (50.0)</td>
</tr>
<tr>
<td>Body mass index (%)</td>
<td>29.3 ± 4</td>
<td>28.8 ± 3</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>25 (31.3)</td>
<td>34 (42.5)</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>48 (60)</td>
<td>44 (55)</td>
</tr>
<tr>
<td>Number of diseased vessel, n (%)</td>
<td>31 (38.0)</td>
<td>35 (43.1)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>66.9 ± 13</td>
<td>63.8 ± 13</td>
</tr>
<tr>
<td>Glycated haemoglobin alcohol (%)</td>
<td>7.4 ± 1.5</td>
<td>7.3 ± 1.4</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dL)</td>
<td>1.13 ± 0.36</td>
<td>1.06 ± 0.27</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>103.7 ± 31.1</td>
<td>103.8 ± 28.4</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>39.4 ± 8.5</td>
<td>40.8 ± 8.8</td>
</tr>
<tr>
<td>Statin use, n (%)</td>
<td>55 (68.8)</td>
<td>65 (81.3)</td>
</tr>
</tbody>
</table>

Values given as percentages or mean ± SD. SES, sirolimus-eluting stent; BMS, bare metal stent; MI, myocardial infarction.
Clinical outcomes at 2 years

Long-term (>2 years) clinical follow-up (median: 26 months interquartile range: 24–29 months) was available in 158 (98.7%) patients. Overall, the MACE rate at 2 years was significantly lower in the SES group. This beneficial effect was obtained at the expense of a significant reduction in the TLR rate after SES implantation. No significant differences in death or MI rates were observed between groups (Table 2).

A total of 12 deaths (7.5%) occurred during the 2-year follow-up period (seven in the SES group and five in the BMS group). In the SES group, two deaths were of cardiac origin (refractory heart failure at 2 months and sudden death at 15 months) and the remaining five were non-cardiac (septic shock at 3 months, stroke at 8 months, bladder cancer at 28 months and two patients died from lung disease: pulmonary embolism at 17 months and end-stage chronic obstructive pulmonary disease at 26 months). In the BMS group, three deaths were cardiac related (cardiac rupture after 2 days and sudden death at 29 days and the last one occurred during cardiac surgery due to the progression of the disease in the left main) and two were non-cardiac related (oesophageal cancer at 13 months and traumatism at 27 months).

In the SES group, three patients presented acute MI, two of them presented with non-Q-wave MI due to progression of the atherosclerosis disease in a non-target coronary segment and the remaining patient presented a Q-wave MI secondary to stent thrombosis. Seven patients in the BMS group presented with MI: three of them were peri-procedural, and in the remaining four the culprit plaque was remote from the target study segment. As a result, atherosclerosis progression accounted for the 75 and 57% of MI cases in the SES and BMS groups, respectively.

The actuarial survival curve for TLR is depicted in Figure 1. The beneficial effect of SES implantation in clinical restenosis was independent of all pre-specified variables: diabetes treatment, gender, vessel location, the use of IIb–IIIa inhibitors, stent size and length, and reference vessel diameter (Figure 2). The predictors of TLR during 2 years by Cox regression analyses were: SES implantation [hazard ratio (HR) 0.12 (95% CI 0.05–0.33), \( P < 0.001 \)], post-procedure minimal lumen diameter [HR 0.36 (95% CI 0.16–0.86), \( P = 0.01 \)], stent length [HR 1.04 (95% CI 1.01–1.08), \( P = 0.02 \)], and baseline creatinine levels [HR 3.46 (95% CI 1.29–9.29), \( P = 0.02 \)]. After the correction of the variance estimates of the HRs, only SES implantation [HR 0.09 (95% CI 0.03–0.29), \( P < 0.001 \)] and baseline creatinine levels [HR 3.79 (95% CI 1.62–8.89), \( P = 0.002 \)] remained as independent predictors of TLR during 2 years.

Revascularization due to atherosclerosis progression

At 2-year follow-up, the need for revascularization owing to atherosclerosis progression occurred in six patients in the

| Table 2 | Univariate analyses of the risk of clinical events at 2 years follow-up |
| --- | --- | --- | --- | --- |
| | Sirolimus-eluting stent (n = 78) | Bare metal stent (n = 80) | Relative risk (95% CI) | P-value |
| Cardiac death, n (%) | 2 (2.6) | 3 (3.8) | 0.8 (0.3–2.4) | 1 |
| MI, n (%) | 3 (3.8) | 7 (8.8) | 0.6 (0.2–1.5) | 0.32 |
| Non-Q-wave | 1 (1.3) | 6 (7.5) | 0.3 (0.04–1.7) | 0.12 |
| Q-wave | 2 (2.6) | 1 (1.3) | 1.4 (0.6–3.1) | 0.62 |
| TLRa, n (%) | 6 (7.7) | 28 (35.0) | 0.3 (0.1–0.6) | <0.0001 |
| PCI | 6 (7.7) | 27 (33.8) | 0.3 (0.1–0.7) | <0.0001 |
| Bypass graft surgery | 0 (0) | 1 (1.3) | Undefined | 1 |
| MACE rateb, n (%) | 10 (12.8) | 33 (41.3) | 0.4 (0.2–0.7) | <0.0001 |
| Stent thrombosis, n (%) | | | | |
| 0–30 days | 0 (0) | 1 (1.3) | Undefined | 1 |
| 31–365 days | 0 (0) | 1 (1.3) | Undefined | 1 |
| >365 days | 3 (3.8)c | 0 (0) | Undefined | 0.12 |

Values are expressed as number of cases (per cent). The analysis was performed on a per patient basis. MI, myocardial infarction; TLR, target lesion revascularization; PCI, percutaneous coronary intervention.

aIn-segment zone.
bNon-hierarchical events.
cIntention to treat analysis.
ses group and in eight patients in the BMS group (7.7 vs. 10.0%; \( P = 0.7 \)). Five patients in the SES group and six in the BMS group were treated with repeat angioplasty, and one additional patient in the SES group and two patients in the BMS group required cardiac surgery. Fifty per cent of the patients required revascularization in the previously treated artery, but in segments remote from the target site.

The rate of total revascularization at 2 years was still significantly lower in the SES group, 15.4% in the SES group and 38.8% in the BMS group, \( P = 0.001 \). The Kaplan–Meier survival free from any cause of revascularization curve is depicted in Figure 3.

Clopidogrel withdrawal and safety

At 1-year follow-up, all (100%) patients were on treatment with clopidogrel. Ninety-five per cent of patients reached 1-year follow-up on concomitant treatment with aspirin. Five per cent of patients were on clopidogrel alone due to contraindications to aspirin. During follow-up, bleeding complications were documented in three patients (1.9%): two patients had gastrointestinal bleeding requiring blood transfusion and additional aspirin withdrawal and one patient presented a mild vitreous haemorrhage that did not require antiplatelet discontinuation.

Stent thrombosis rate up 1-year follow-up was 0% in the SES group. During this period, there were two stent thromboses in the BMS group: the first occurred while the patient was on dual antiplatelet therapy, whereas the latter occurred 1 week after transient clopidogrel withdrawal. This patient was diagnosed with colon carcinoma 1 month after the enrolment; clopidogrel was withdrawn 2
months after the index procedure due to the need of abdominal surgery. (Table 2).

After clopidogrel withdrawal (from 1 to 2 years), 3 patients allocated to the SES group presented with stent thrombosis. One patient presented thrombosis in a BMS implanted prior to the inclusion in the trial. This patient had a completed remission of a breast cancer 5 years ago and was in treatment with tamoxifen since then. The second patient presented a non-fatal acute anterior MI secondary to a newly developed coronary aneurysm (Figure 4). Interestingly, the IVUS examination of this patient at 9 months revealed a lack of neointimal proliferation with stent struts well apposed to the arterial wall, suggesting that aneurysm has appeared between 9 and 25 months. In both cases, the stent thrombosis occurred within the first month after clopidogrel withdrawal. The remaining patient who died suddenly was adjudicated as stent thrombosis. One patient presented thrombosis in a BMS and was in treatment with tamoxifen since then. The patient had a completed remission of a breast cancer 5 years ago and was in treatment with tamoxifen since then. The second patient presented a non-fatal acute anterior MI secondary to a newly developed coronary aneurysm (Figure 4). Interestingly, the IVUS examination of this patient at 9 months revealed a lack of neointimal proliferation with stent struts well apposed to the arterial wall, suggesting that aneurysm has appeared between 9 and 25 months. In both cases, the stent thrombosis occurred within the first month after clopidogrel withdrawal. The remaining patient who died suddenly was adjudicated as stent thrombosis. The IVUS study at 9-month showed a late-acquired incomplete stent apposition. No additional stent thrombosis was observed in the BMS group (Table 2).

Discussion

The main findings of this study were: (i) the extended clinical benefit of SES in reducing the need for TLR up to 2-year follow-up, (ii) the marked cumulative rate of revascularization due to atherosclerosis progression observed in both groups (10.0% in the BMS group and 7.7% in the SES group), and (iii) the increase in the incidence of late stent thrombosis following clopidogrel discontinuation.

At 2-year follow-up, SES implantation demonstrated a marked reduction in TLR compared with BMS, which was independent of diabetic treatment. The long-term benefit of SES implantation has been previously described in the general population.16-17 To date, retrospective subgroup analyses of pivotal clinical trials have suggested that SES may be effective in diabetic patients at long-term follow-up.9,10 However, these trials only included lesions of low-to-moderate risk for restenosis. The DIABETES trial extends the long-term benefit of SES in a population of higher risk for restenosis as it included chronic total occlusions (13%), small vessels (2.34 mm average reference diameter), long lesions (43% longer than 20 mm), multivessel disease (65%), and nephropathy (32%).13

The independent predictors of TLR at 1 year included SES implantation and baseline creatinine levels. Renal dysfunction is associated with accelerated atherosclerotic disease progression18 and increased restenosis and mortality rates after percutaneous coronary revascularization procedures19,20. Importantly, diabetes is the leading cause of nephropathy21 and their combination further enhances the cardiovascular risk. Recently, patients with diabetic nephropathy have shown to have an increased risk for target vessel failure after BMS implantation.22 In our study, 40% of TLR in the SES group occurred in patients with nephropathy (serum creatinine $> 1.5$ mg/dL).

Diabetic patients typically exhibit accelerated progression of atherosclerotic disease.4 This phenomenon has classically been tarnished by the long-term outcomes after percutaneous coronary interventions, compared with surgery in patients with diabetes mellitus.23,24 This is the first study in the drug-eluting stent era that has addressed the impact of disease progression after SES implantation in diabetics. Of interest, progression of atherosclerotic disease was responsible for 50% of the total revascularization rate in the SES group at 2 years. Loutfi et al.25 previously reported that disease progression contributed to 57% of repeat revascularization procedures in diabetic patients with multivessel disease treated with BMS. Besides, we documented the development of acute coronary syndromes during follow-up in both groups. In this regard, culprit lesions remote from the target site were identified in 57 and 75% of the MIs that occurred during follow-up in the BMS and SES groups, respectively. Therefore, the more aggressive and diffuse nature of atherosclerotic disease in patients with diabetes mellitus underscores the importance of more aggressive treatment strategies with broad systemic effects in order to prevent acute ischaemic complications in diabetic patients.

Late stent thrombosis is a major concern after DES implantation. In the present study, thrombosis of the SES was observed only after clopidogrel discontinuation in one patient with documented late-acquired incomplete stent apposition at 9 months and in another patient with a coronary aneurysm developed at the site of the stented segment. The IVUS substudy of this trial15 showed that SES implantation is associated with an increased incidence of incomplete stent apposition in diabetic patients. Further, in some cases, it has been associated with aneurysm formation.
formation.26 Both entities may represent a different phase of the same process, which involves a hypersensitivity reaction to the stent polymer.26 On the other hand, two of the three BMS thromboses occurred within 30 days after clopidogrel discontinuation. Of note, in both patients, current or previous history of malignancy was present. The relationship between cancer and stent thrombosis has been reported.27–29 The hyper-coagulability status associated with malignancy and diabetes mellitus along with clopidogrel withdrawal may play a role in the development of stent thrombosis. In our trial, clopidogrel was maintained for 12 months in both groups. This decision was based on the inherent prothrombotic milieu of diabetic patients, the concomitant risk for renal insufficiency, the high prevalence of acute coronary syndromes in this population, and the potential need for small stents, among others. This policy goes in line with a recent report from the American Heart Association/American College of Cardiology that highly stressed the importance of 12-month dual antiplatelet treatment in patients receiving drug-eluting stents.30 In addition, we advise to assess aspirin resistance before clopidogrel withdrawal and in the event of either aspirin resistance or demonstration of late incomplete stent apposition during follow-up, indefinitely prolong dual antiplatelet.

Limitations

For the purposes of the study, atherosclerosis progression was clinically assessed and only lesions requiring new revascularization were considered. Therefore, the current study probably infra-estimates the true overall incidence of disease progression of the entire coronary tree.

In the present study, impaired renal dysfunction was found to be an independent predictor of TLR at 2 years. However, diabetics with severe renal disease (creatinine clearance < 30%) were excluded from the study, and thereby these results cannot be extrapolated to the population with end-stage renal disease. In addition, microalbuminuria and other microvascular complications such as retinopathy have not been addressed. Thus, further studies are warranted to evaluate the prognostic implications of microvascular complications of diabetes mellitus after SES implantation.

This study is underpowered to demonstrate differences in death or MI. Thus, further studies with a larger number of patients are needed to assess the impact that SES implantation in diabetic patients may have on such hard endpoints.

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References


