Diabetic revascularisation by coronary angioplasty: is one stent better than another?

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Abstract

As confidence in the use of drug-eluting stents (DES) increases, they are being used in patients with progressively more complex disease. Diabetes is still an independent risk factor for restenosis along with lesion length and reference vessel diameter.

This article gives an overview of recent stenting trials, including those with more complex disease such as DIABETES, PORTO 1 and TAXUS V. It also looks at head-to-head randomised controlled trials of sirolimus-eluting stents against paclitaxel-eluting stents: ISAR-DESIRE, SIRTAX, ISAR-DIABETES and REALITY. These give a better indicator of comparative efficacy than meta-analyses which include differing patient populations and trial designs. Finally, studies comparing angioplasty with surgery are considered.

Key words: percutaneous coronary intervention, diabetes, paclitaxel, sirolimus, complex lesions, drug-eluting stents.

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Introduction

Diabetes is an increasingly common condition in the developed world. Currently, more than 1.8 million people have diagnosed diabetes in the UK, and it is thought that as many as a million more remain undiagnosed. Since approximately 65% will die from cardiovascular complications, it is not surprising that diabetic coronary disease has been the focus of so much recent attention.

Few would doubt the positive impact that drug-eluting stents have had upon the treatment of coronary artery disease. As confidence in the use of drug-eluting stents increases, an ever larger and more challenging cohort of patients are receiving percutaneous coronary intervention (PCI) in place of coronary artery bypass grafting (CABG). Diabetes was identified as an independent risk factor for target lesion revascularisation (TLR) and cardiac death during the bare-metal stent (BMS) era;[1-3] and continues to be an independent risk factor for restenosis in patients given drug-eluting stents (DES).[4,5] There are two other pre-procedural risk factors for restenosis, namely lesion length and reference vessel diameter.[6-8]

Randomised controlled trials comparing DES with BMS have demonstrated that DES are better at preventing both angiographic and clinical restenosis, leading to greatly reduced rates of overall major adverse cardiac events (MACE). Comparisons of trial data have been complicated, however, by differences in timing of follow-up, patient inclusion and exclusion criteria, and complexity of disease. When considering the relative benefits of one drug-eluting stent over another, the demonstration of statistically significant differences is made more difficult by the low rates of TLR and MACE found in both sirolimus- and paclitaxel-eluting stents. Very large patient numbers, or patients with much more complicated disease, are needed to power clinical trials adequately, and the interpretation of diabetic data at present relies on meta-analyses.

Early drug-eluting stent trials

Initial trials comparing DES with BMS controls preferentially selected patients at the low-risk end of the spectrum, with larger diameter, shorter vessels and less multivessel disease. Such populations are not representative of the complex disease often encountered in diabetics. Such selective recruitment was partly due to reluctance among clinicians to accept stenting as a viable treatment option for diabetic patients with complex disease. In addition, optimal evidence-based use of platelet inhibition was not practised at that time. This patient subset was suitable for demonstration of the clear superiority of DES over BMS but it is very difficult to draw comparisons between performance of different DES based on these data.

A combined meta-analysis of 292 diabetic patients within initial trials involving sirolimus-eluting stents (Ravel®, Sirius®, E-Sirius®, C-Sirius®, Direct® and Svelte®) demonstrated a nine-month binary angiographic in-stent restenosis rate (BAR) of 5.7%, compared with 50.6% in the BMS arm, as measured by quantitative coronary angiography (QCA) (figure 1). This translated to a 5.8% rate of TLR and a 8.9% rate of MACE, compared with 22.3% and 26.2%, respectively, in the BMS group.[9,10] Likewise, a meta-analysis of the 216 diabetic patients within the TAXUS II, IV and VI trials has demonstrated a 5.1% rate of BAR, compared with 33.1% in bare-metal controls. This translated to TLR rates of 5.6% and 20.7%, respectively.[11] Whilst absolute

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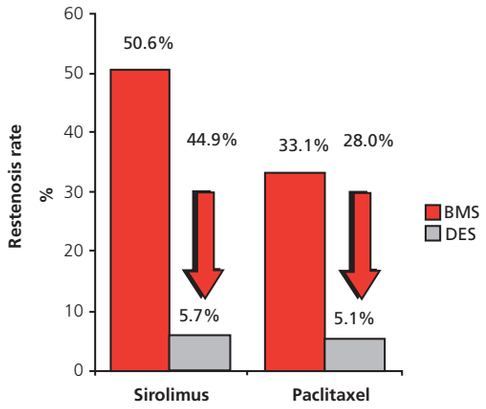
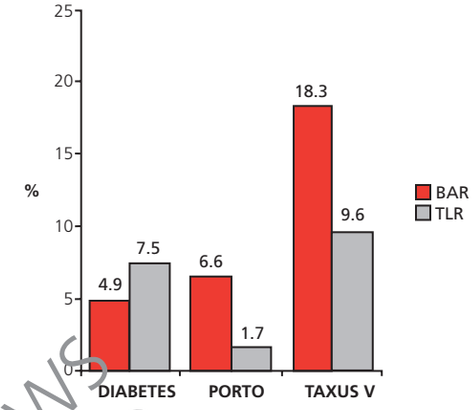
Figure 1. Comparison of binary angiographic in-stent restenosis rates in early trials



Key: BMS = bare-metal stent; DES = drug-eluting stent

Figure 2. TLR and BAR rates in diabetic subsets of patients with moderately complex disease in the DIABETES and PORTO 1 studies and the TAXUS V analysis



Key: TLR = target lesion revascularisation; BAR = binary angiographic in-stent restenosis rate

rates of restenosis between DES in the meta-analysis appear similar, it is interesting to note the increased relative reduction in BAR in sirolimus stents when compared with their BMS controls. This is influenced by the comparative efficacy of the BMS controls used, but may be also due to differences in the patient populations recruited.

ENDEAVOR II, a recently presented trial, assessed the efficacy of the new Endeavour® drug-eluting stent against the Driver® bare-metal stent. Only 18% of the patients in ENDEAVOR II had diagnosed diabetes, which is far lower than the rate found in other recent trials. Among the diabetics, neither patients with very small (reference vessel 2.74 mm) nor with very long (average lesion length 14.05 mm) lesions were recruited. Despite this, TLR at nine months was 7.5% in the Endeavour arm versus 15.2% in the Driver arm. Late luminal loss in diabetics receiving the Endeavour® stent was higher than one might have hoped at 0.68 mm.[12,13]

Diabetics in complex DES versus BMS trials

Both sirolimus- and paclitaxel-eluting stents are very effective at preventing restenosis, and it is when looking at trials involving complex disease that we are likely to see any true differences emerging. Diabetes, total stented length and post-procedural stent diameter are all demonstrated independent risk factors for TLR and in part help govern the complexity of a given trial.[3,14,15] Over recent years patients with more complex disease and a greater prevalence of diabetes have been included in trials. Furthermore, trials recruiting only diabetic patients, including DIABETES, ISAR-DIABETES and PORTO 1, have attempted to address the efficacy of drug-eluting stents in this high-risk group. TLR and BAR data are shown in figure 2.

DIABETES study

This independent study, conducted at four centres in Spain, was the first randomised controlled trial of patients with moderately complex disease to recruit only diabetics. Sirolimus-eluting stents were compared with a BMS control, and 70 patients were recruited to each arm. Average reference vessel diameter was 2.34 mm and lesion length 15 mm. Angiographic follow-up was performed at nine months, and demonstrated very low rates of restenosis (4.9%) when compared with BMS controls (31%). Angiographic findings translated to low rates of TLR (7.5%) and MACE (11.3%) at 12-month follow-up in the sirolimus-eluting stent arm, which were in stark contrast to those found in the BMS arm (32.1% and 40.7%, respectively).[10]

PORTO 1 study

This was carried out in a moderately complex, non-randomised series of 120 diabetic patients with small vessel disease (average diameter 2.04 mm) who received sirolimus-eluting stents. Lesion length was, however, short at 11.16 mm, with a notably low incidence of mutivessel disease (12.5% of patients had two- or three-vessel intervention), and 91.6% of patients received only one stent. Angiographic follow-up at eight months demonstrated a binary restenosis rate of 6.6%. Six-month clinical follow-up revealed an incredibly low TLR of 1.7% and combined MACE of 5.0%.[16]

TAXUS V

In the TAXUS V diabetic subgroup analysis, 356 patients (30.8%) were included, of whom 183 were randomised to receive paclitaxel stents and 173 to receive BMS controls. This group of diabetic patients had disease of moderate complexity, with an average reference vessel diameter of 2.67 mm and lesion length of 17.4 mm. Both clinical and angiographic follow-up were performed at nine months; at this point TLR was 17.5% in the con-

Figure 3. Binary in-stent restenosis rates in head-to-head clinical trials

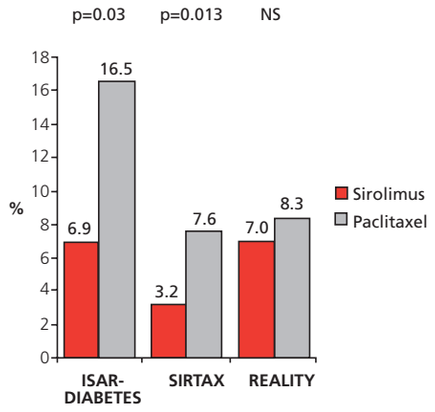
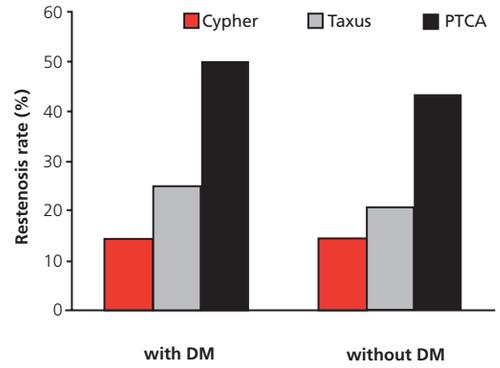


Figure 4. Restenosis rates in the ISAR-DESIRE trial



Key: DM = diabetes mellitus; PTCA = percutaneous transluminal coronary angioplasty

trol *vs.* 9.6% in the paclitaxel group, with 38.4% and 18.3% binary restenosis rates, respectively.[17]

Head-to-head randomised controlled trials

To date there have been four major randomised controlled trials comparing sirolimus-eluting stents directly with paclitaxel-eluting stents. By analysing the results of these trials we can get a better idea of comparative efficacy without the substantial problems posed to meta-analyses by differing patient populations and trial designs. The diabetic subgroup analyses from both SIRTAX and REALITY are not yet available (see figure 3).

ISAR-DIABETES

The ISAR-DIABETES trial recruited 125 diabetic patients to both sirolimus-eluting and paclitaxel-eluting arms. Average lesion length and reference vessel diameter were well matched, at 13.8 mm/2.7 mm (sirolimus) and 12.4 mm/2.75 mm (paclitaxel). Angiographic follow-up at six months revealed restenosis rates of 6.9% and 16.5%, respectively, resulting in a TLR rate of 6.4% in the sirolimus arm compared to 12.2% with paclitaxel.[18]

REALITY

REALITY was a complex trial which randomised patients to a sirolimus (n=684) or paclitaxel (n=669) arm, and incorporated 378 diabetic patients. The primary end point of the trial was angiographic in-lesion binary restenosis. Average reference vessel diameters were identical at 2.40 mm, and lesion lengths were well matched at 16.96 mm/17.31 mm, respectively. This translated to a binary angiographic in-stent restenosis rate of 7.0% versus 8.3% for the paclitaxel arm, which was not statistically different.[19]

SIRTAX

This study randomised 1,012 patients to a sirolimus- or paclitaxel-eluting arm; of these patients 201 had diagnosed diabetes. This was an all-comers' trial, with a patient population that included those with acute coronary syndromes, chronic total occlusions and bifurcations. Lesions between 2.25 to 4.0 mm were included and there was no limit on number of lesions or length. The trial was not particularly complex, with average reference vessel diameter and lesion lengths well matched at 2.82 mm/2.83 mm and 12.37 mm/13.42 mm, respectively, for sirolimus- and paclitaxel-eluting arms. The binary restenosis rates in-stent were 3.2% for the sirolimus-eluting stents versus 7.6% for the paclitaxel stents. This translated to a decrease in combined death, myocardial infarction and TLR of 6.2% versus 10.8% respectively, largely driven by an increased TLR in the paclitaxel arm of 8.3%.[20]

ISAR-DESIRE

The ISAR-DESIRE (Intracoronary Stenting and Angiographic Results – Drug-eluting Stents for In-stent Restenosis) study was an independent randomised trial that showed DES provide results superior to those achieved with standard percutaneous transluminal coronary angioplasty (PTCA) in the treatment of in-stent restenosis. Secondary analysis also suggests an advantage for sirolimus-eluting stents over paclitaxel-eluting stents in terms of clinical restenosis rates.[21]

In ISAR-DESIRE a total of 300 patients (28% diabetic) with in-stent restenosis (ISR) were randomised to receive sirolimus-eluting (Cypher®) or paclitaxel-eluting (Taxus®) stents or to PTCA. The primary study end point was the BAR, and repeat angiography at six months was performed in 92% of patients. Figure 4 presents the angiographic restenosis rates for patients with and without diabetes.[22]

Late luminal loss and restenosis

Late luminal loss has been shown in multivariate analysis to be an independent predictor of subsequent TLR rates.[23] It seems probable that the relationship between late loss and TLR will be greater in smaller vessels, where small decreases in diameter

Table 1. Mean in-stent late luminal loss in major clinical trials

	Sirolimus	Paclitaxel
DIABETES	0.09 mm	-
PORTO 1	0.10 mm	-
ISAR-DIABETES	0.19 mm	0.45 mm
REALITY	0.09 mm	0.31 mm
SIRTAX	0.13 mm	0.25 mm
TAXUS VI	-	0.39 mm

Key messages

- Diabetes is an independent risk factor for restenosis, even with increased use of drug-eluting stents
- Percutaneous coronary intervention is now used in patients with increasingly complex lesions
- There appears to be a clear trend towards reduced rates of restenosis and late luminal loss in diabetics given sirolimus-eluting stents compared to those who receive paclitaxel-eluting stents

lead to significant increases in resistance to flow. The impact of late loss is likely to be greater in diabetics, who have a greater prevalence of complex, small-vessel disease. Data from a number of clinical trials (table 1) demonstrate lower late loss with sirolimus-eluting stents compared to paclitaxel-eluting stents.

Surgery versus angioplasty for multivessel diabetic coronary artery disease

Results from recent trials indicate that the use of DES should be mandatory in complex lesions. There remains, however, considerable debate about the level of complexity that requires surgical rather than percutaneous revascularisation. A number of clinical trials comparing bypass surgery to angioplasty have attempted to clarify these issues. In the balloon angioplasty and BMS era, these trials tended to favour surgical revascularisation for diabetics. More recently, results from the diabetic subset in ARTS II suggested that the differences are substantially less than they have been in the past, though the patients recruited were relatively selective and the use of GP IIb/IIIa inhibitors was suboptimal.

ARTS II

The ARTS II trial enrolled 607 patients to receive multivessel sirolimus-eluting stents, including 158 diabetics. The recently presented results demonstrated a combined MACE rate of 15.7% and TLR of 12.5% at 12-month follow-up. These figures were contrasted with the earlier ARTS I CABG arm, which demonstrated a MACE rate of 14.6% and TLR of 4.6%, respectively.[24,25] It is interesting to note how the level of complexity for these trials has changed as the technology has advanced. In the BENESTENT trial in Rotterdam the total stented length was 10 mm, in ARTS I PCI it was 48 mm, and in ARTS II it was 73 mm. Between ARTS I and II the proportion of diabetics and multivessel disease increased notably, from 19% (27% triple-vessel disease) to 26% (54% triple-vessel disease). Future trials addressing surgery versus angioplasty will concentrate on more complex disease, with particular focus on diabetics.

CARDia

CARDia is a non-inferiority trial randomising diabetic patients in the United Kingdom and Ireland to complex stenting (n=300) or CABG (n=300) in order to compare current PCI with current CABG techniques in this difficult subset of patients. BMS were used initially in the PCI arm but patients have been receiving sirolimus-eluting stents since September 2003. This change of protocol was driven by the rapid shift in practice towards DES during the trial. The trial design stipulates the inclusion of multivessel disease or complex single-vessel disease, and marks a move towards excluding those patients with low-complexity disease from the analysis. The trial is on course for completion by mid-2006.

The FREEDOM trial is another large trial based on a similar design to CARDia. It will be randomising diabetic patients to either drug-eluting stents (sirolimus/paclitaxel) or CABG.

Conclusion

Numerous clinical trials have demonstrated that DES lead to a dramatic improvement in both angiographic and clinical end points when compared with their bare-metal counterparts. As a result of their success, the subsequent determination of DES superiority has been complicated by the large numbers of patients necessary to power studies which demonstrate clear statistical differences. Both stent platforms are deliverable and associated with excellent procedural success, and rates of acute thrombosis are low. When used in patients at the lower-risk end of the spectrum, both brands of stent provide excellent short- to intermediate-term results. Nevertheless, when analysing data from diabetic patients in trials to date, there would appear to be a clear trend towards reduced rates of restenosis and late luminal loss in sirolimus-eluting stents when compared with paclitaxel stents. It remains to be seen what contribution late luminal loss will make to rates of clinical restenosis in the long term.

Conflict of interest

None declared.

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