Revascularisation and the diabetic patient: the potential role of drug-eluting stents

David Barrow, a medical journalist with a special interest in interventional cardiology, discusses the potential benefit of drug-eluting stents in relationship to the revascularisation of the diabetic patient.

Background

It has been estimated that 13% to 25% of the patients undergoing coronary revascularisation procedures have diabetes and the diabetic patient continues to face higher mortality rates than non-diabetic patients after revascularisation. There is much debate on the preferred method of revascularisation in the diabetic patient: percutaneous transluminal intervention (PCI) or coronary artery bypass graft surgery (CABG).

Type 2 diabetes

More than 20% of subjects admitted to coronary care units for acute coronary syndromes have known – or on this occasion – newly-detected diabetes. Impaired glucose tolerance (IGT) is even more common. And yet recent improvements in the management of cardiovascular diseases have still to be seen in the diabetic population. The prevalence of ischaemic heart disease in diabetics is also very high. Regardless of age, the diabetic patient has a much higher incidence of coronary artery disease than the general population, a fact borne out by evidence from the historic trials, such as RITA, EAST, CABRI and BARI.

The BARI trial

The BARI trial concluded that compared with CABG, an initial strategy of PCI for the treatment of multi-vessel coronary artery disease revealed no difference in survival and was associated with a higher need for late (up to five years) repeat revascularisation. The BARI investigators also concluded that in the diabetic subgroup population, there was an associated higher mortality at five years. But in the BARI Registry those patients who were eligible but did not consent to a randomised PTCA versus CABG trial were treated equally well with whichever treatment option their physician chose. Moreover, diabetic status did not affect the results.

This may have been due to those patients with the most severe anatomy being treated with surgery creating a bias in the patient selection. Available evidence from the CABRI trial also suggests that there is uncertainty as to whether revascularisation by PCI or CABG is preferable.

Stenting or surgery?

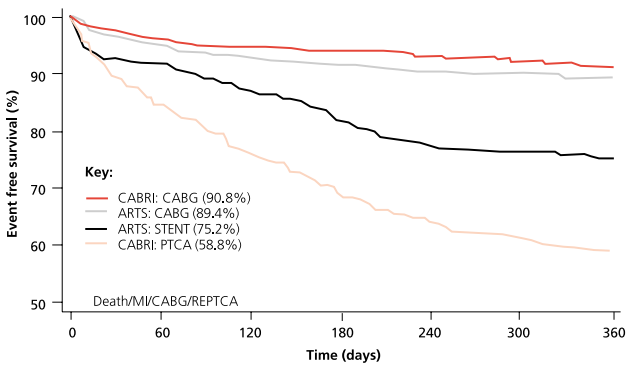
Will improvements in stent technology level the playing field between surgery and angioplasty in diabetic patients? (see figure 1). We still do not know whether drug-eluting stents will fulfil the early promise first demonstrated by Sousa and Serruys who showed encouraging 12-month follow-up data at Euro-PCR in 2001. Six-month follow-up results of RAVEL with a 16% diabetic subset of patients were unprecedented with zero restenosis, zero late loss (recognised as a major predictor of long-term outcome following PCI) and zero target vessel revascularisation. One year follow-up of RAVEL confirmed continued clinical benefit in terms of an absence of reintervention and no clinical evidence of a 'catch-up' phenomenon.

Preliminary clinical results presented at an American Heart Association meeting in 2001 show the potential for the sirolimus-eluting stent to markedly reduce in-stent restenosis (see figure 2) in patients with coronary artery disease. At four-month follow-up, researchers from the Dante Pazzanese Institute of Cardiology, Sao Paulo, Brazil, reported extremely low in-stent late loss of 0.08 mm in minimum lumen diameter in the 25 patients treated at this hospital. In-stent late loss is a sensitive and specific measure of the amount of tissue prolif-

Glossary of trial acronyms

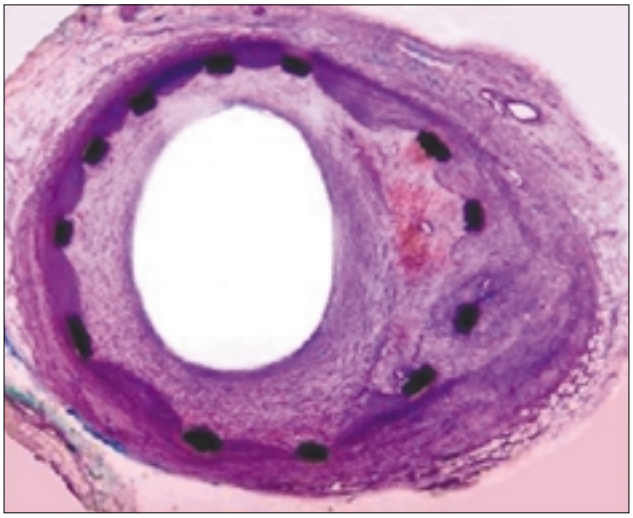
ARTS	Arterial Revascularisation Therapy Study
ASPECT	Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis
BARI	Bypass Angioplasty Revascularisation Investigation
CABRI	Coronary Angioplasty *vs.* Bypass Revascularisation Investigation
CURE	Clopidogrel in Unstable angina to prevent Recurrent ischemic Events
EAST	Emory Angioplasty versus Surgery Trial
ELUTES	European Evaluation of Paclitaxel-Eluting Stent
RAVEL	A Randomised Study with the Sirolimus-eluting Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with *de novo* Coronary Artery Lesion
RITA	Randomised Intervention Treatment of Angina
SIRIUS	Sirolimus-eluting Stent in Coronary Lesions Study
SOS	Stent Or Surgery trial Europe

Figure 1. Event-free survival in the CABRI and ARTS studies



From ARTS/CABRI; Cardiology, European Society of Cardiology, Rotterdam, 1999

Figure 2. Restenosis: a problem of excessive neointimal hyperplasia



eration that can result in re-blockage of the vessel.

Additionally, the study's results show 0.0% (zero) restenosis, 0.0% (zero) target lesion revascularisation (TLR), no thrombosis, and no deaths. The reference vessel diameter was 2.8 mm, with a mean diameter stenosis of 7.7%. Results were documented using intravascular ultrasound (IVUS) and quantitative coronary angiography evaluated by independent core laboratories.

Speaking on behalf of the team from the Dante Pazzanese Institute, Dr Eduardo Sousa, one of the pioneers of drug-eluting stents said: "We were particularly impressed by the efficacy of the sirolimus-eluting stent against a wide variety of restenotic lesions, especially since many of the lesions were long and tortuous and 24% of the patient population were diabetics."

Dr Alexandre Abizaid, a co-worker of Dr Sousa, highlighted the scale of the problem by saying: "In-stent restenosis is a difficult condition to treat and will occur in 20–30% of patients receiving a conventional intracoronary stent. In the USA alone, it is estimated that 150,000 patients will suffer from in-stent restenosis each year."

Additional data concerning drug-eluting stents have been presented at several international meetings. Speaking at the 2001 American Heart Association meeting in Anaheim, USA, UK interventional cardiologist, Dr Tony Gershlick, Glenfield Hospital, Leicester, presented six-month follow-up results from ELUTES. This dose-finding study of paclitaxel coated on to a conventional intracoronary stent involved a total of 192 patients and consisted of four dosing arms ranging from 0.2 to 2.7 micrograms of paclitaxel and one control arm.

It revealed a restenosis rate of 3.1% in those patients who received a stent coated with the highest concentration of paclitaxel and reconfirmed the angiographic findings of a previous paclitaxel-coated stent study (ASPECT), although some observers believe that it did not show any clinical benefit between the control and the high dose arm. Moreover, there is a view among cardiologists that, due to the small sample size in each individual arm of ELUTES, additional studies will be required in order to confirm these preliminary results.

Latest results

By comparison, data presented at the 2002 Transcatheter Cardiovascular Therapeutics conference in Washington, USA, in September support the previous encouraging results from RAVEL. In a more complex patient population consisting of 26% diabetics (n=279), small vessels and complex lesions, the SIRIUS investigators reported consistent reductions in late loss and restenosis in the diabetic subgroup (see table 2). Co-principal investigator Dr Martin Leon, Lenox Hill Hospital, New York, USA, said: "Diabetic patients represent one of the challenging patient groups at a high risk of restenosis. On an absolute basis, the diabetic patient subset in SIRIUS realised a greater treatment effect compared with the bare metal control, than did the overall patient cohort".

He added: "When reviewing efficacy by subgroup, the data suggest that for every 100 diabetic patients treated with a sirolimus-eluting stent we will prevent 15.4 target lesion revascularisation events. Similarly, we can prevent almost 33 cases of restenosis in every 100 diabetic patients treated with this drug-eluting stent". Dr Leon noted that these data will help to drive the economic argument in favour of drug-eluting stents.

But available data from SOS and ARTS, although not clear-cut, suggest that surgery remains the best option for the diabetic patient.

Professor Patrick Serruys and his co-workers from the Thoraxcenter, Rotterdam, The Netherlands, compared the 208 diabetic patients with the 996 non-diabetic patients taking part in ARTS. After one year, mortality in the diabetic subset of the patient population who received angioplasty

Table 2. Clinical outcomes (follow-up at nine months) in the diabetic subgroup of the SIRIUS study

	Sirolimus (n=131)	Control (n=148)	p-value
Major adverse cardiac event			
In-hospital	1.5%	1.4%	0.99
At follow-up	7.6%	23.6%	<0.001
Target lesion revascularisation	6.9%	22.3%	<0.001
Target vessel revascularisation	10.3%	25.0%	0.002
Target vessel failure	12.2%	27.0%	0.003

Key messages

- 20% of subjects admitted to coronary care units for acute coronary syndromes have known, or on this occasion, newly-detected diabetes
- Diabetes is one of three key predictors for restenosis
- Revascularisation of the diabetic patient continues to represent a major challenge
- Drug-eluting stents may offer a viable alternative to coronary artery bypass graft surgery
- The SIRIUS trial with a sirolimus-eluting stent shows consistent reductions in late loss and restenosis in diabetic patients

and stenting was double that of those undergoing bypass surgery (6.3% *vs.* 3.1%). For stroke, this trend was reversed – mortality rates of 6.3% were seen in the CABG group compared to 1.8% in the stent group. Commenting on these results, Professor Serruys acknowledged that diabetic patients show, in general, poor clinical outcome in the stent group compared to the CABG group. This led him to say that surgery, even with its attendant risk of cerebrovascular accident may be preferable to stenting, an opinion he saw no reason to change following the two-year follow-up data from ARTS. Professor Serruys is confident, however, that the use of adjunctive therapies, such as glycoprotein IIb/IIIa inhibitors and drug-eluting stents, might reverse these outcomes.

Adjunctive therapies

This view appears to be supported by evidence from PCI-CURE, a companion study of CURE, which according to the investigators, demonstrated the early and long-term benefits of clopidogrel on top of standard therapy including aspirin in patients with acute coronary syndrome undergoing PCI. Dr Shamir Mehta, McMaster University, Ontario, Canada, and principal investigator of PCI-CURE, reported an overall reduction of 31% in cardiovascular death or heart attack in those patients given clopidogrel prior to treatment and continued for up to one-year post procedure.

But, according to Dr Spencer King, The Atlanta Cardiovascular Research Institute, Atlanta, USA, if we compare the more modern ARTS trial results using stenting in the diabetic population, to the BARI trial results, at one year we get a much better idea as to what progress has been made in recent years. At one year follow-up in BARI, the mortality rate was much higher in the overall population and favoured surgery. But in ARTS, by one year, the mortality was lower although the directionality was the same. There was no significant difference between both groups but the stented patients were not doing quite as well as the surgery group.

The big difference was in revascularisation. The BARI angioplasty patients had a very high reintervention rate (surgery or angioplasty) whereas the ARTS patients had a much reduced need for reintervention. So ARTS reduced the need for reintervention by about 50% reflecting improving results for interventional therapies.

Nevertheless, Dr King concedes that even with stents and glycoprotein IIb/IIIa glycoprotein inhibitors, diabetic patients remain at higher risk than non-diabetic patients.

But when asked if physicians should abandon stenting for a diabetic patient, Dr King was emphatic in his response: "No", explaining that there are a number of reasons why interventional cardiologists can select percutaneous intervention for diabetics with multi-vessel disease.

BARI II, a new randomised US study involving 2,600 diabetic patients who are not severely symptomatic but who have documented coronary disease and myocardial ischaemia, hopes to find out if the five-year survival rate of patients who are asymptomatic or mildly symptomatic with ischaemic heart disease can be extended by revascularisation. Although the patients will be randomised to either medical therapy or intervention, the intervention will not be randomised to angioplasty or surgery and interventional cardiologists predict that most will be treated by angioplasty. The study will also assess whether diabetes should be managed initially by trying to get the haemoglobin A1c as low as possible with insulin or whether improving insulin sensitivity would be the most efficacious way to prolong the life of these patients.

Conclusion

In conclusion, the evidence base for revascularisation and the diabetic patient continues to grow. It remains to be seen if the introduction of drug-eluting stents, coupled to the use of adjunctive therapy such as glycoprotein IIb/IIIa inhibitors will contribute to the continued evolution of percutaneous coronary intervention in those with diabetes or whether surgery will remain the best option.

References

These are available on request from the editorial department.