Percutaneous coronary intervention for revascularization of the diabetic patient

The field of interventional cardiology has progressed rapidly in recent years with the advent of new technology and expanding role of adjunctive pharmacology. This article provides an overview of both current and historical approaches to treating coronary artery disease in the diabetic patient.

At present there is a lack of consensus among cardiologists as to the best treatment strategy for diabetic patients with multi-vessel coronary artery disease. Traditionally this group of patients would have undergone coronary artery bypass surgery (CABG) based largely on the results of the Bypass Angioplasty Revascularisation Investigation (BARI) trial (BARI Investigators, 1996). This was an early study with some methodological faults. The field of interventional cardiology, however, has been revolutionized since BARI by the introduction of new and more effective technology, especially bare metal stents and drug-eluting stents, and adjunctive pharmacology. Consequently recent years have seen a progressively more complex subset of patients undergoing percutaneous revascularization with a corresponding increase in use of drug-eluting stents. This change is reflected in the roll out to clinical practice of the results of trials which now include a greater proportion of diabetics with complex, diffuse small vessel disease.

Why are diabetic patients different?

The short answer is that it is unclear which of the probable factors that could in theory predict excess atheroma formation play a role – it is likely that a combination of a number of factors is responsible. What is clear, however, is that diabetes mellitus is a common and chronic disease with a high cardiovascular mortality. At present over 1.8 million people have been formally diagnosed with diabetes mellitus in the UK and it is estimated that around a million more remain undiagnosed.

Over recent years the incidence of type 2 diabetes has risen dramatically associated with the increasing epidemic of obesity and metabolic syndrome in western countries. Treatment options in such patients are difficult and, irrespective of whether surgical or percutaneous revascularization is chosen, diabetes is an independent predictor of adverse outcome. The mechanisms underlying this process include a complicated interplay of insulin resistance, hyperglycaemia, hyperlipidaemia and hypertension along with abnormalities of haemostasis, all of which ultimately lead to endothelial dysfunction and accelerated atherogenesis.

Insulin resistance and hyperglycaemia

Insulin resistance is often clinically silent and often predates the onset of type 2 diabetes by decades (De Fronzo, 1997). It is characterized by reduced insulin-mediated glucose uptake (Alberti and Zimmet, 1998), increased serum insulin concentrations and eventually hyperglycaemia (Balkau and Charles, 1999). Diabetes mellitus is known to be a strong risk factor for the development of both micro- and macrovascular disease; however, insulin resistance in non-diabetic subjects also correlates with an increased incidence of subsequent myocardial infarction and death (Hedblad et al, 2002). Hyperglycaemia increases susceptibility to wound infection in CABG patients, but is also thought to be one of the major contributors to endothelial dysfunction characterized by impaired smooth muscle relaxation and impaired coronary flow (Woodman et al, 2005).

Platelet function and thrombosis

Increased platelet aggregation and thrombotic tendencies have long been recognized in diabetic patients. Nevertheless the underlying pathology is complex and involves diminished platelet sensitivity to anti-aggregates such as prostacyclin and nitric oxide, enhanced expression of glycoprotein IIb/IIIa receptors (Tschoepe et al, 1990, 1995), and elevated levels of fibrinogen (Missov et al, 1996), factor VII, Von Willebrand factor (Duncan et al, 1999) and plasminogen activating factor type 1.

Inflammation and intimal hyperplasia

Both diabetes and insulin resistance are associated with low grade inflammation which plays a major role in all stages of atherogenesis and the development of intimal hyperplasia (Libby, 2002). In addition, small elevations in the concentrations of serum C-reactive protein among other acute phase proteins have been associated with the

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subsequent development of atherosclerosis (Ridker et al, 1997). Diabetes is associated with elevated levels of various growth factors, and highly atherogenic low density lipoprotein particles often driven by hyperglycaemia which contribute to an exaggerated intimal response (Ridker et al, 1998).

Advanced glycosylation end products

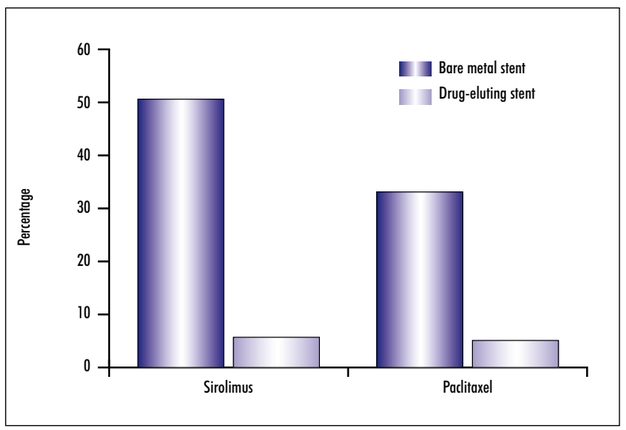
Diabetics undergo a process of non-enzymatic glycation, in which reducing sugars are covalently attached to free amino groups and ultimately form advanced glycosylation end products (AGEs). There are receptors for AGEs (RAGEs) on monocytes, leading to enhanced inflammatory reactions and the release of chemokines and cytokines. Smooth muscle cell RAGE overexpression leads to increased cell turnover through upregulation of the tumour suppressor genes and to the production of excess intracellular matrix.

There clearly are many culprits in the production of excess atheroma and excess vessel response to injury-pathways in diabetics. By its very nature percutaneous coronary intervention (PCI) acts through vessel wall injury and the response to this injury has in many ways been the limitation of the percutaneous procedure, with excess recurrence in stented patients. Thus repeat procedure rates have been higher with PCI than with surgery. This and the believed lower mortality in diabetics undergoing coronary artery surgery has led to the belief that all diabetics should undergo the more invasive procedure.

Characteristic coronary disease

Patients with diabetes typically develop a diffuse calcified pattern of coronary disease involving a greater proportion of small vessels than typically found in non-diabetics. Small distal vessel disease is particularly challenging for the attachment of surgical grafts, while small reference vessel diameter, longer lesion length and the presence of diabetes are all demonstrated independent risk factors for restenosis in coronary artery stents (Cutlip et al, 2002; Moses, 2004; Moussa et al, 2004). Heavily calcified lesions present a technical challenge to interventional cardiologists and are associated with increased in-hospital event rates (Wilensky et al, 2002).

Figure 1. Meta-analysis of binary angiographic restenosis rates in early drug-eluting stent vs bare metal stent trials.



Changing patient populations and complexity of clinical trials

Following the advent of drug-eluting stents we are now seeing far lower rates of both clinical and angiographic restenosis than were found in the balloon angioplasty and bare metal stent era (Grube, 2004; Holmes et al, 2004; Sabate, 2005) (*Figure 1*). As confidence in their use has increased, changes in clinical practice have followed at great pace, and now a progressively more complex set of patients are recruited into clinical trials.

Diabetes, post-procedural stent diameter and total stented length are all independent risk factors for restenosis in coronary stents (Holmes et al, 2004; West et al, 2004; Mauri et al, 2005) and in part help govern the complexity of a given trial. Meta-analyses of stenting trials and comparisons between surgical and percutaneous intervention are made difficult by differing patient populations and trial designs. This is compounded by changes in pharmacological therapies with the introduction of clopidogrel and glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, which are particularly beneficial in diabetic PCI, reducing the frequency of acute complications and subsequent reintervention (Topol et al, 1999; Ibbotson et al, 2003; Mehilli et al, 2004).

Initial trials comparing CABG with balloon angioplasty in multivessel disease

Trials comparing balloon angioplasty with CABG had very small subsets of diabetic patients (*Table 1*) and specific data regarding diabetic control were sparse. In the landmark trial comparing long-term clinical outcome (BARI), a total of 1829 patients with documented ischaemia and two- or three-vessel disease were randomized between 1989 and 1992 along with 2010 whom consented to registry follow up. Of these patients 353 randomized patients had treated diabetes along with 339 present in the registry. It is interesting to note that the 94 patients with diet-controlled diabetes were included into the non-diabetic analysis. When looking specifically at the diabetic subset, the 5-year cardiac mortality was significantly higher in the balloon angioplasty arm (23.4% *vs* 8.2%). This benefit was confined to those surgical patients who received left internal mammary grafts distal to left anterior descending (LAD) artery lesions (81%) and was not seen in those receiving either venous or radial grafts.

In parallel the diabetic CABG and PCI registry patients manifested statistically similar but much lower rates of cardiac death (7.5% *vs* 6%). On subset analysis there were some angiographic differences present in registry diabetics receiving PTCA, notably a lower prevalence of triple vessel disease ($P<0.001$) and proximal LAD lesions ($P<0.001$) (Detre et al, 1999; Brooks et al, 2000). These results demonstrated that when physician preference determined treatment modality, survival was higher than when patients were randomized to either arm.

BARI was not designed to look specifically at diabetics and optimal diabetic control was not specified, neither were GPIIb/IIIa inhibitors nor clopidogrel used. Critically it reported during an era that pre-dated the current widespread stent use. Clearly when considering the registry data, along with the exclusion of diet-controlled patients, the advantage of CABG over angioplasty cannot be extrapolated to all diabetics. The Emory Angioplasty Versus Surgery Trial (EAST) reported no overall mortality benefit in patients receiving CABG at 8-year follow up; however, a small statistically insignificant increase in mortality among the diabetic subset became apparent from 5 years onwards in the balloon angioplasty arm (Weintraub et al, 2000). These trials should now be considered of historical interest only.

Table 1. Trials comparing angioplasty and bare metal stenting with coronary artery bypass grafting

Trial	Reference	No. of diabetics	Total no. in trial	Recruitment
BARI (Percutaneous transluminal coronary angioplasty)	BARI Investigators (1996)	353	1829	1988–91
CABRI (Percutaneous transluminal coronary angioplasty)	CABRI Trial Participants (1995)	122	1054	1988–92
EAST (Percutaneous transluminal coronary angioplasty)	King et al (1994)	59	392	1987–90
RITA (Percutaneous transluminal coronary angioplasty)	RITA Trial Participants (1993)	62	1011	1988–91
ERACI I (Bare metal stent)	Rodriguez et al (1993)	13	127	1988–90
ERACI II (Bare metal stent)	Rodriguez et al (2001)	77	450	1996–8
ARTS I (Bare metal stent)	Serruys et al (2001)	208	1205	1996–7
SOS (Bare metal stent)	SoS Investigators (2002)	150	988	1996–8

ARTS = Arterial Revascularisation Therapy Study; BARI = Bypass Angiolasty Revascularisation Investigation; CABRI = Coronary Angioplasty versus Bypass Revascularisation Investigation; EAST = Emory Angioplasty versus Surgery Trial; ERACI = Argentine randomised trial of coronary angioplasty with stenting versus coronary artery bypass surgery in multivessel disease; RITA = Randomised Intervention Treatment of Angina trial; SOS = Stent or Surgery

Bare metal stenting *vs* CABG in diabetics

The introduction of bare metal stents overcame a number of the mechanisms leading to restenosis including elastic recoil and trials at this time demonstrated significantly improved outcomes when comparing stenting to angioplasty (Kiemeneneij et al, 2001). This was in part driven by far fewer patients now requiring emergency CABG with its high operative mortality. In order to ascertain whether this advance in technology would impact on survival in complicated multivessel disease, a number of trials at the time compared coronary stenting with bypass surgery. Again these trials were not set up specifically to look at diabetic patients, and were thus underpowered to detect real differences between the groups (*Table 1*).

ARTS I (Arterial Revascularisation Therapies Study) was a multicentre randomized controlled trial and had the largest subset of diabetic patients. The overall primary endpoint at 12 months demonstrated no significant difference in death, myocardial infarction or stroke between CABG and stenting. When considering the diabetic subset, 1-year mortality was not statistically different between the two arms. Rates of revascularization were predictably higher in the PCI arm (columns 1 and 2 in *Table 2*) (Abizaid et al, 2001) but this represented a dramatic reduction compared with balloon angioplasty when rates of revascularization could be as high as 40–50%. At 5-year follow up there was a small statistically insignificant increase in mortality in the stenting arm (13.4% *vs* 8.3%) (Serruys, 2005). It is

Table 2. Comparison of the diabetic subset from the ARTS trials

		ARTS I (PCI)	ARTS I (CABG)	ARTS II (PCI)
Number of patients		112	96	159
Proportion of diabetics		19%	16%	26%
Total stented length		53 mm	–	74 mm
Repeat revascularization	CABG	8.0%	1.0%	3.1%
	PCI	14.3%	3.1%	9.4%
Death		6.3%	3.1%	2.5%

ARTS = Arterial Revascularisation Therapy Study; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention. From Morice (2005)

important to note that GPIIb/IIIa inhibitors were used at low levels and diabetic patients on the trial did not necessarily receive them.

Diabetics are thought to have an increased thrombotic tendency, which would explain data supporting improved outcome with such agents and one might speculate that increased use would have helped to prevent stent thrombosis (and its associated mortality) and reduce the incidence of micro-infarction which leads to late death as well as reducing revascularization need (Topol et al, 1999; Ibbotson et al, 2003; Mehilli et al, 2004). The Stent or Surgery (SoS) trial recruited 488 patients to PCI, of which 14% had diabetes mellitus, and similarly reported no statistical difference in incidence of death, or Q wave myocardial infarction but noted an increased incidence of revascularization in the PCI group (21% *vs* 6%) at 2-year median follow up (SoS Investigators, 2002).

An interesting meta-analysis of 1228 trial patients receiving bare metal stents has demonstrated that while non-target lesions less commonly led to revascularization than stented target lesions in the first year, they dominated subsequent events in years 2–5 post procedure (Cutlip et al, 2004). It has long been recognized that plaque stability plays a key role in the development of acute myocardial infarction, and that smaller apparently more benign lesions on angiography contribute heavily to long-term rates of revascularization. As such no patient should undergo any form of intervention without aggressive treatment of all identifiable cardiac risk factors if we are truly to offer prolonged benefit.

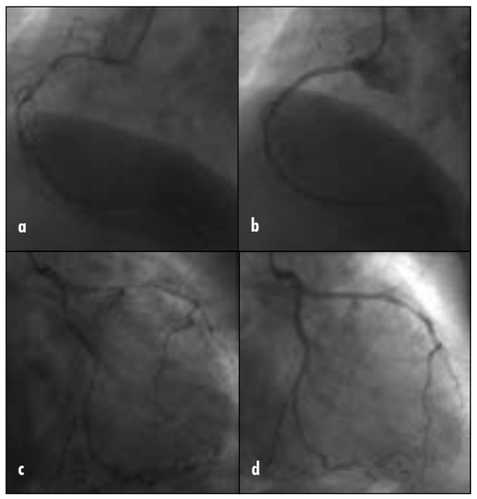
The drug-eluting stent era

Drug-eluting stents prevent in-stent restenosis by inhibiting injury-induced smooth muscle cell proliferation, and inflammatory cell activity thus reducing neointimal hyperplasia within the stent and at its margins (*Figure 1*). While reduced intimal proliferation is of benefit in maintaining stent patency, the delayed endothelialization has led to concerns over acute stent thrombosis. Patients are now usually treated with clopidogrel for up to 1 year to prevent such events, and based on current trial and registry data, rates of thrombosis are low (Butts, 2005; Sousa, 2005).

Early trials comparing drug-eluting stents to bare metal controls demonstrated a clear advantage in both diabetics (*Figure 2*) and non-diabetics. A wealth of data from randomized controlled trials demonstrates a dramatic reduction in both clinical and angiographic restenosis, along with a marked decrease in late luminal loss. As the use of drug-eluting stents has increased, trials have progressively included patients of increased complexity, recruiting increased numbers of diabetics, with disease in smaller vessels and longer lesions.

Other studies have focussed solely on the diabetic patient rather than consider post-hoc analyses. These studies include the DIABETES, ISAR-SWEET, ISAR-DIABETES, PORTO1 and BARI-IId trials. Other studies have compared drug-eluting stents with surgery and data related to diabetics can be extracted. Thus the ARTS II trial was a prospective registry assessing the performance of sirolimus-eluting stents in dual and triple vessel disease. The aim was to recruit a similar patient cohort to that in the previous ARTS I trial so that comparisons relating to performance could be made. Despite the trial protocol, the patient population in ARTS II was generally more complex than in ARTS I with a marked increase in the proportion of triple vessel disease and presence of diabetes, albeit with a decreased incidence of previous myocardial infarction. Considering the diabetic subset analysis there appears no significant difference in mortality or combined major adverse cardiac events at 12 months. However, revascularization was still higher in the ARTS II PCI arm when compared with ARTS I (CABG) (*Table 2*). This relative decrease in revascularization when compared with the ARTS I PCI reflects an important trend (Morice, 2005) but clearly in diabetic patients there is still work to do.

Figure 2. Preprocedural angiograms in a 70-year-old female patient with type 2 diabetes mellitus and triple vessel disease. The films demonstrate (a) tight stenoses of the proximal and mid right coronary artery, and (c) tight stenoses of the proximal left anterior descending and circumflex arteries. Post procedural pictures (b, d) following the insertion of six drug-eluting stents demonstrate vastly improved coronary perfusion. The procedure was uncomplicated and the patient remains asymptomatic without any evidence of subsequent adverse event.



Trials assessing drug-eluting stent efficacy in diabetics

While there are now a large number of percutaneous trials demonstrating an impressive reduction in target lesion revascularization when using drug-eluting stents, the numbers of diabetics are small and so conclusions are largely drawn from meta-analysis (Butts et al, 2005). There is little doubt that in the types of patients recruited both paclitaxel- and sirolimus-eluting stents dramatically reduce rates of restenosis when compared with bare metal stents.

While efficacy of drug-eluting stents has been proven in de novo single vessel disease there is still very little data comparing drug-eluting stents and CABG in patients with multivessel disease and diabetes. When considering the data available from trials assessing drug-eluting stent efficacy in diabetics, along with data from the ARTS II series it is anticipated that rates of revascularization will be dramatically reduced. The benefit of optimal glycaemic control in diabetes has long been accepted, however, there are limited data from stenting trials to suggest that poor glycaemic control contributes to increased rates of restenosis. In the Taxus II trial (Colombo et al, 2003) those diabetics with a HbA_{1c} (glycosylated haemoglobin) <7.0% had no target lesion revascularization while those with a value greater then 7.0% had a target lesion revascularization rate of 3.8%.

In order to address this question two landmark trials (CARDia and FREEDOM) are underway. The CARDia trial is a multicentre randomized controlled trial recruiting diabetics with both complex single vessel and multivessel disease to either CABG or stenting with sirolimus-eluting stents within the UK. At present over 400 of the 600 patients have been recruited and detailed data regarding diabetic control and HbA_{1c} are being recorded both at baseline and follow up. The FREEDOM trial is a large multicentre (>2000 patients) trial recently commenced, addressing a similar question but recruiting in both America and Europe. Patients are randomized to either a sirolimus-eluting stent arm or CABG arm.

Conclusions

Recent evidence with drug-eluting stents suggests no difference in mortality at 12 months compared with CABG and revascularization rates in high-risk diabetics have fallen dramatically since the era of angioplasty. Data on long-term outcome in diabetic patients treated with drug-eluting stents are lacking, particularly when compared to CABG. It does appear, however, that many diabetic patients now have a viable treatment alternative to surgery, and decisions should be made following open discussion of the pros and cons of both treatments with the patient. Many factors other than raw statistics are used in the decision-making process, and the option of a minimally invasive strategy appeals to many with increasing numbers opting now for percutaneous intervention.

With the appropriate use of antiplatelet agents and antithrombins together with fastidious technique to achieve excellent (drug-eluted) stented result then non-surgical treatment of diabetic patients with coronary artery disease is a justifiable alternative to CABG. BJHM

Conflict of interest: Dr J Butts is a trial coordinator in the CARDia trial.

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KEY POINTS

- Coronary artery bypass grafting in the balloon angioplasty era was the preferred method of revascularization in diabetics leading to improvements in both mortality and rates of revascularization.
- The use of drug-eluting stents has revolutionized the field of interventional cardiology, and dramatically reduced rates of angiographic and clinical restenosis.
- Current evidence to date suggests that there is no excess mortality when diabetics are treated with sirolimus-eluting stents rather then bypass surgery although numbers are low. Revascularization is still more common than following surgery, but far less frequent than in the past.
- If needed most patients can be further revascularized by percutaneous techniques following restenosis and so avoid surgery.
- Additional data are still needed to confirm long-term prognosis following stenting but short to intermediate term results are very encouraging.
- The FREEDOM (Future Revascularisation Evaluation in Patients with Diabetes: Optimal Management of Multivessel disease) and CARDia (Coronary artery revascularisation in diabetes) trials are looking specifically at diabetics in greater numbers, and will provide valuable additional information about the use of drug-eluting stents in diabetic multivessel disease compared to surgery.
- Interventional treatment is not a substitute for meticulous diabetic control and evidence based use of medications such as statins and angiotensin-converting enzyme inhibitors. Improved exercise tolerance will be far more beneficial in the absence of retinopathy, neuropathy and dialysis.

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