Has anything changed in multivessel coronary artery revascularization in diabetes since BARI?

Akhil Kapur, Davide Bartolini, Kevin J. Beatt

Department of Cardiology, Hammersmith Hospital, National Heart and Lung Institute, Imperial College School of Medicine, London, UK

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Diabetic patients have an increased risk of coronary disease partly due to a higher frequency of associated risk factors including hypertension and hyperlipidemia but also from specific risks largely resulting from insulin resistance, hyperinsulinemia and hyperglycemia. This has resulted in a greater need for revascularization. Despite this there are few randomized data comparing surgery and angioplasty in patients with diabetes. The evidence to define the best operative strategy is limited, mainly confined to a subanalysis of the BARI trial suggesting the superiority of surgery in patients with multivessel disease. However there has been in Europe a wide increase in multivessel angioplasty, even in diabetic patients. This article discusses the higher risk of patients with diabetes, the data comparing surgery and angioplasty and outlines the advances in angioplasty since BARI.

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Address:

Dr. Kevin J. Beatt

Department of Cardiology
Hammersmith Hospital
National Heart and Lung Institute
Imperial College School of Medicine
London W12 0HS
UK
E-mail:
k.beatt@imperial.ac.uk

Diabetes is on the increase

There are now 200 million people with type 2 diabetes in the world[1]. In developed countries the prevalence of diabetes in the general population is almost 5%, rising up to 20% in persons over 60 years of age[2]. The risk of a major event in diabetic patients with non-coronary disease is more than double that of non-diabetic patients with coronary heart disease[3,4]. The Framingham study showed that diabetes increased the relative risk of coronary heart disease by 66% in men and 203% in women followed up for 20 years once effects such as age, smoking, blood pressure and cholesterol had been controlled for[5]. Projections suggest that 30% of all revascularizations will be in patients with diabetes by 2015 but sound scientific evidence on how to treat these patients is lacking and the question of what form of revascularization is most beneficial is still controversial.

Data comparing surgery and angioplasty in diabetics is limited

There is little in the way of randomized data comparing surgery and angioplasty in patients with diabetes even though patients with diabetes mellitus have an increased requirement for coronary revascularization. The evidence from previous trials demonstrates that diabetic patients do worse with both coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI)[6]. Evidence to suggest the best operative strategy is limited, mainly confined to a subanalysis of BARI (Bypass Angioplasty Revascularization Investigation)[7]. This trial showed a highly significant mortality benefit of CABG over PCI albeit in a non-prespecified subset of just 353 patients out of the total of 1829 patients recruited into the trial. Despite this limitation the results of the BARI trial have been most influential in CABG being considered the treatment of choice for diabetic patients with multivessel disease. However, in at least some centers in Europe there has been an increase in multivessel angioplasty in diabetic patients. This may be justified by the fact that in the BARI trial patients were recruited between 1988 and 1991 when perceptions and treatments were fundamentally different from the treatments offered today.

The results from BARI have rarely been replicated mainly because of the small sizes of the subsets in the other interventional trials (Table I)[8-16]. During the bare metal stent era ARTS (Arterial Revascularization Therapies Study), which recruited between 1996 and 1997, addressed the issue of multivessel stenting vs surgery. The quadruple endpoint of death, myocardial

Table I. Subsets of patients with diabetes in the major interventional trials.

Trial	No. patients	No. diabetics	Recruitment period	Sample size allows comparison of CABG vs PCI in diabetes at 1^0 endpoint?
BARI[7]	1829	353	1988-1991	Yes
RITA[8]	1011	62	1988-1991	No
CABRI[9]	1054	122	1988-1992	No
EAST[10]	392	59	1987-1990	No
ERACI[11]	127	13	1988-1990	No
ERACI II[12]	450	77	1996-1998	No
ARTS[13]	1205	208	1996-1997	Yes
GABI[14]	359	43	1986-1991	No
SoS[15]	988	142	1996-1998	No

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

infarction (MI), cerebrovascular accident and repeat revascularization at 1 year favored surgery over angioplasty in the trial as a whole and in the diabetic subset with high rates of repeat revascularization in the PCI arm as with all randomized studies of this type to date. Although it should be noted that the rate of repeat revascularization after index angioplasty had decreased compared to the pre-stent era. There was no difference in the triple endpoint of death, MI and cerebrovascular accident between PCI and CABG in terms of the general population of patients but there was a trend in favor of surgery in the small diabetic subset, which numbered 208 out of a total of 1205 patients, although it must be remembered that in this trial only 4% of patients in the PCI arm received glycoprotein (GP) IIb/IIIa inhibitors, important because they have been shown to reduce death and MI particularly in patients with diabetes as discussed below[17,18].

Why are diabetic patients different?

It is well known that diabetic patients have a higher frequency of associated risk factors including hypertension and hyperlipidemia[19]. In addition there are specific risks to diabetic patients largely resulting from insulin resistance, hyperinsulinemia and hyperglycemia[20]. These include dyslipidemia (characterized by increased concentrations of small dense LDLs, triglyceride-rich VLDLs and low concentrations of HDLs), endothelial dysfunction (characterized by increased expression of plasminogen activator inhibitor-1 and cellular adhesion molecules), and impaired vasomotor activity related to decreased availability of nitric oxide. Other risk factors include oxidative stress (increased concentrations of markers such as oxidized LDLs and F2-isoprostanes), inflammation (resulting in increased expression of markers such as fibrinogen and C-reactive protein), abnormalities in coagulation and fibrinolysis (resulting in overproduction of fibrinogen and expression of plasminogen activator inhibitor-1 and tissue-type plasminogen activator), and glycation of proteins (resulting in the formation of advanced glycation end-products in LDL and collagen within the arterial wall, which have a variety of proatherogenic effects).

The increased risk of diabetic coronary heart disease

These patients have a greater need for revascularization and for repeat revascularization after their initial procedure.

As well as the increased risk associated with diabetes there is evidence that the manifestations of coronary heart disease are more severe in patients with diabetes. An analysis of baseline characteristics in diabetic vs non-diabetic patients revealed that those with diabetes had a higher incidence of triple vessel disease (46 vs 40%, respectively, $p = 0.05$) and left ventricular dysfunction, defined as an ejection fraction < 50% (31 vs 20%, $p = 0.001$) resulting in a significantly lower 5-year survival[7]. In the angioplasty substudy of the GUSTO-IIb (Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes)[21] the incidence of multivessel disease was much higher in diabetic patients, compared to those without diabetes (45.3 vs 32.4% , $p = 0.006$), and the mean ejection fraction was lower (48 vs 51%, $p = 0.003$). In the same study diabetes was associated with a poorer outcome (death or reinfarction), both at 30 days (13.1 vs 8.5%, $p = 0.0001$) and at 6 months (18.8 vs 11.4%, $p = 0.0001$)[22]. These differences in clinical features of coronary heart disease are reflected in angiographic findings. Typically diabetic patients have more diffuse, multivessel and distal coronary disease, smaller reference vessels, poorer coronary collateral circulation, and more frequent left main stem disease[23-26]. The topic of revascularization in diabetes therefore deserves separate consideration.

Advances in percutaneous coronary intervention since BARI

There is no doubt that both CABG and PCI have advanced technically in recent years. It is also true that the field of coronary angioplasty in its routine practice has changed more substantially than has CABG, although the increased use of both off-pump coronary artery surgery and of arterial conduits holds promise.

Stenting. The STRESS (Stent Restenosis Study) and Benestent (Belgian Netherlands Stent) trials demonstrated that in selected patients coronary stents reduce the risk of restenosis and subsequent clinical events[27,28], a reduction most marked in diabetic patients[29]. In one study of diabetic patients, coronary stenting was associated with a better 6-month angiographic outcome and a better 4-year clinical outcome compared to balloon angioplasty alone[30]. The balloon angioplasty patients experienced a significant reduction in ejection fraction at 6 months (2.4 ± 10.9%, $p < 0.02$), while no change was observed in the stent group. At 4 years, a significant reduction in the combined endpoint of cardiac death and non-fatal MI was observed in the stent group (14.8 vs 26.0%, $p < 0.02$), attributed to a lower rate of occlusive restenosis and preservation of left ventricular function. The requirement for repeat revascularization was 52.1 vs 35.4% ($p < 0.001$) in the balloon and stent group respectively. Another study, however, confirmed that even with stenting, diabetic patients still had a less favorable outcome at 1 year. MI-free survival was significantly reduced in the diabetic group (89.9 vs 94.4%, $p < 0.001$) and the incidence of both restenosis (37.5 vs 28.3%, $p < 0.001$) and stent vessel occlusion (5.3 vs 3.4%, $p = 0.037$) was significantly higher in diabetic patients. The heterogeneity of diabetes was demonstrated by Abizaid et al.[31] who investigated the clinical outcome following coronary stent implantation in insulin requiring (IR) patients, non-insulin requiring diabetic (non-IR) patients, and non-diabetic patients. IR patients were at a significantly higher risk for subsequent target lesion revascularization (28%) compared with non-IR patients (17.6%) and non-diabetic patients (16.3%). Late cardiac event-free survival was significantly lower in IR patients (60%) compared with non-IR patients (70%) and non-diabetic patients (76%). Multivariate analysis showed that insulin requirement was an independent predictor for 1-year major adverse cardiac events (MACE) (odds ratio 2.05, $p = 0.0002$).

Glycoprotein IIb/IIIa inhibitors. Newer pharmacological interventions, such as GPIIb/IIIa inhibitors and clopidogrel, improve the outcomes of PCI[32,33]. Several trials have shown that abciximab and other GPIIb/IIIa inhibitors improve acute outcome and that this benefit may be sustained in the long term[34-36]. In particular the combination of stents and GPIIb/IIIa inhibitors appears to be most effective, especially in patients with diabetes[32].

The role of adjunctive periprocedural pharmacotherapy has been examined in several trials[32,36,37]. In the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting) study, the composite of death, MI, or target vessel revascularization (TVR) at 6 months was reduced from 25 to 13% (a 48% reduction, $p = 0.005$) in diabetic patients treated with abciximab and stenting as opposed to stenting alone[38]. The combined benefit of stenting and abciximab in diabetic patients undergoing PCI persisted at 1-year follow-up. The death and MI rate was reduced from 16.3 to 6.8% at 1 year in diabetic patients treated with abciximab compared to placebo, with cardiac event rates reduced to the level seen in non-diabetic patients[39]. A pooled analysis of three abciximab trials EPIC (Evaluation of c7E3 for the Prevention of Ischemic Complications), EPILOG (Evaluation in PTCA to improve Long-Term Outcome with Abciximab GPIIb/IIIa Blockade) and EPISTENT demonstrated that abciximab decreased the 1-year mortality in diabetic patients from 4.5 to 2.5% ($p = 0.031$) and in non-diabetic patients from 2.6 to 1.9% ($p = 0.1$)[18].

In the only head-to-head comparison of GPIIb/IIIa antagonists, the TARGET trial (Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial) randomized 5308 patients to tirofiban or abciximab before PCI stenting[40,41]. Abciximab was superior to tirofiban in reducing the 30-day primary endpoint of composite death, MI or TVR (6.0 vs 7.6%, $p = 0.038$). Both tirofiban and abciximab offered similar protection against death, MI or TVR at 6 months (14.8 vs 14.3%, p = NS). Among diabetic patients randomized to tirofiban (n = 560) and abciximab (n = 557), the incidence of death, MI, or TVR at 30 days was similar (6.2 vs 5.4% respectively, $p = 0.54$). Both tirofiban and abciximab were associated with comparable event rates, including similar rates of 6-month TVR (9.5 vs 11.1%, $p = 0.366$) and 1-year mortality (2.1 vs 2.9, $p = 0.436$). The results of the ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) trial revealed that eptifibatide reduced death, MI, and urgent TVR at 2 and 30 days in patients undergoing coronary stenting. The 1-year results showed a significant reduction in MI and a non-significant reduction in death with a similar benefit in reducing cumulative events in diabetic and non-diabetic patients treated with eptifibatide[42,43].

In summary the combined use of GPIIb/IIIa inhibitors and stents in diabetic patients, at least with abciximab and tirofiban, appears to reduce the level of risk that diabetic patients undergoing PCI have to that of non-diabetic patients receiving placebo. Whether the results achievable with this regimen are comparable to those achieved with modern CABG can only be answered by a prospective randomized trial.

Drug-eluting stents. A major limitation of PCI is in-stent restenosis and a subsequent requirement for further revascularization procedures, reducing the overall impact of its initial success as a treatment strategy, when compared with CABG. That restenosis may become a thing of the past was first intimated by 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) trial suggesting that the use of sirolimus-coated stents during PCI can reduce or even prevent restenosis[44].

Data from the multicenter, randomized, double-blind SIRIUS (Sirolimus-Coated Bx Velocity Stent in the Treatment of Patients with de Novo Coronary Artery Lesions) study have recently been published[45]. The inclusion criteria were more liberal than RAVEL and allowed multilesion stenting, which occurred in a quarter of patients. The primary endpoint was target vessel failure, which included cardiac death, MI, or TVR at 9-month follow-up. After 9 months, 8.6% of the patients receiving the Cypher stent reached the primary endpoint of target vessel failure, compared with 21.0% in the control group. In the sirolimus group, in-stent restenosis was 2.0%, and in-lesion restenosis was 9.1%, these results confirming the potent antirestenotic effects of Cypher stents. In the diabetic subset, which comprised 279 out of 1058 patients, 12.2% of the patients receiving the Cypher stent reached the primary endpoint, compared to 27.1% in the control group demonstrating a comparable benefit for diabetic patients also. Thus the relative reduction in recurrent events seen with sirolimus vs control remained constant but the absolute values for restenosis, target lesion revascularization and other indices were higher in both groups for diabetic patients and diabetes remained an independent predictor of restenosis and target lesion revascularization.

These results were replicated by the recently published TAXUS IV study[46], a study comparing the paclitaxel-coated stent vs bare metal stenting. The target lesion revascularization rate was reduced from 9.8% in the control group to 2.4% in the paclitaxel stent group in the study as a whole, and from 16.0% to 5.2% in the patients with diabetes with a suggestion that the benefit was as great with IR patients as with non-IR patients a benefit not demonstrated in the SIRIUS trial although in both studies the numbers in the subset of insulin-treated patients are very small so it is difficult to draw firm conclusions.

Post-revascularization risk factor modification. The use of drug-eluting stents reduces the further requirement for revascularization and abciximab reduces the early death and MI rates in PCI patients with diabetes. However these therapies will not deal with the cause of poorer late outcomes in diabetic patients, which is increased disease progression. By bypassing some of this new disease surgery affords some protection. However aggressive lipid-lowering treatment[47] and long-term oral antiplatelet drugs[33] after angioplasty are improvements that can complement a percutaneous strategy to slow down the accelerated disease progression seen in diabetic patients. The LIPS study (Lescol Intervention Prevention Study) showed the significant benefits of very early initiation of lipid-lowering therapy with fluvastatin (80 mg/day) in patients undergoing their first PCI[47]. During 3.9 years of follow-up, compared with patients in the placebo group, those in the fluvastatin group had a significant reduction (26.7 vs 21.4%, $p < 0.01$) in the incidence of MACE. Of note is that patients with diabetes (12% of the study population) experienced a 47% reduction of MACE as compared to placebo ($p = 0.041$) and patients with multivessel disease (37% of the study population) experienced a 34% reduction in MACE ($p = 0.011$).

Future studies

In the United Kingdom the CARDIA (Coronary Artery Revascularization in Diabetes) trial is underway. It is an investigator initiated study and is the first randomized prospective study of its type specifically in patients with diabetes and is designed to address the hypothesis that optimal PCI with stenting and abciximab is not inferior to up-to-date CABG as a revascularization strategy for diabetic patients with multivessel or complex single vessel coronary disease. The primary endpoint is a composite of death, non-fatal MI and cerebrovascular accident at 1 year. Twenty-one centers in the United Kingdom and Ireland have begun to recruit 600 diabetic patients. Patients randomized to PCI will now also receive drug-eluting stents (Fig. 1). Total arterial revascularization is encouraged in the surgical arm and subanalysis of both these patients and those receiving drug-eluting stents will be undertaken. The

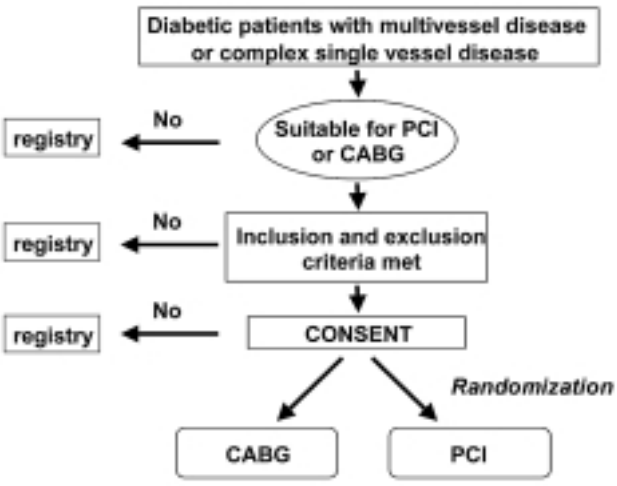

Figure 1. *CARDIA trial design. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.*

FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) study in the United States is also due to commence and is a larger head-to-head study comparing surgery with drug-eluting stents in patients with diabetes although use of a GPIIb/IIIa inhibitor is not mandatory in the PCI arm. ARTS 2 is a registry which will provide data on the use of drug-eluting stents in multivessel disease in the general population of patients and BARI 2D is a 2 × 2 comparison of firstly revascularization by either strategy vs aggressive medical therapy for coronary disease and secondly whether treatment with an insulin-sensitizing regimen or an insulin-providing regimen is preferred.

Conclusion

Diabetic patients are a high-risk group of patients for revascularization whose numbers are increasing. Traditionally surgical revascularization has been preferred in diabetic patients with multivessel coronary disease. They benefit from antiplatelet therapy especially GPIIb/IIIa inhibitors when treated percutaneously and derive equivalent benefit to non-diabetic patients from drug-eluting stents although diabetes remains an independent risk factor in the latest drug-eluting stent trials. Although it is clear that diabetic patients are a high-risk group who deserve separate study they are a heterogeneous group whose risk varies and is higher in those who are insulin-treated. Another group of patients who may in the future also deserve special attention and who are thought to be at high risk for increased events is the group with glucose intolerance or insulin resistance without frank diabetes, although these patients are currently not easily identified. Indeed it has been shown that hyperinsulinemia in patients with impaired glucose tolerance induces greater intimal hyperplasia after stent implantation[48]. As well as drug-eluting stents insulin sensitizers in the form of the oral thiazolidinediones hold out early promise for reducing restenosis in diabetic patients when combined with a percutaneous strategy[49]. The results of further studies in this area as well as those outlined above such as the CARDIA study and the FREEDOM trial are eagerly awaited.

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