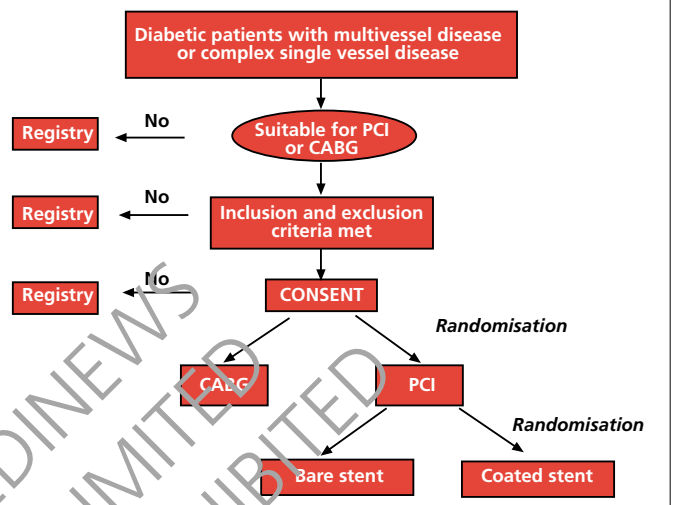
Why do we need the CARDia trial?

Introduction

The Coronary Artery Revascularisation in Diabetes (CARDia) trial is an investigator-initiated study and is the first prospective study designed specifically to address the hypothesis that optimal percutaneous coronary intervention (PCI) with stenting and abciximab is not inferior to up-to-date coronary artery bypass grafting (CABG) as a revascularisation strategy for diabetics with multivessel or complex single vessel coronary disease. The primary end point is the well-established composite of death, non-fatal myocardial infarction (MI) and cerebrovascular accident (CVA) at one year. Twenty centres in the UK have begun to recruit 600 diabetics, with more than 100 patients already randomised to either PCI or CABG. Patients randomised to PCI will be further randomised to a comparison of bare metal against rapamycin-coated stents (figure 1). Recruitment is due to be completed in 2004.

Figure 1. Design of the CARDia trial



The burden of diabetes is increasing

The burden of type 2 diabetes is rising rapidly. There are now 200 million people with this condition in the world and the total is projected to increase to 300 million by 2025.[1] In the United Kingdom alone 2.5 million people have diabetes. With an ageing and an increasingly obese population this will rise and it is thought that there will be three million people in the UK diagnosed with the condition by 2010.[2] The prevalence of diabetes in the general population in developed countries is almost 5%, rising to 20% in persons over 60 years of age.[3]

Large epidemiological studies have shown that the risk of coronary heart disease (CHD) is increased two- to six-fold in patients with type 2 diabetes compared with that in non-diabetic individuals.[4,5] Furthermore, in diabetics the risk of a major event is at least double that in non-diabetics with CHD. The Framingham study showed that diabetes increased the relative risk of CHD 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.[6] It has been estimated that more than 30% of all revascularisations will be performed in patients with diabetes by 2015. The question of which form of revascularisation is the most beneficial remains controversial.

There are few data comparing CABG versus PCI in diabetics

Patients with diabetes mellitus have an increased requirement for coronary revascularisation but there are few randomised data on revascularisation in patients with diabetes. There is some evidence from previous trials that diabetics do worse with both CABG and PCI. Evidence to suggest the best operative strategy is limited, mainly confined to a sub-analysis of the North American Bypass Angioplasty Revascularization Investigation (BARI).[7] This suggested a mortality benefit of CABG over PCI.

Since the results of the BARI trial were published, CABG has been considered the treatment of choice for diabetics with multivessel disease. Despite this there has been an increase of multivessel angioplasty in these patients in some centres in the UK. This may be justified by the fact that the BARI trial patients were recruited from 1988 to 1991. For PCI this represents a different era, and one which preceded stenting and other adjunctive therapies in PCI. It has also been noted that the BARI study's results in diabetics were in a subset of 353 out of the total of 1,829 patients recruited into the trial and that this analysis was not prespecified. Despite these factors the difference between the two modalities was highly significant and there is little doubt that in this previous era surgery was the treatment of choice.

Few data have replicated these results, mainly because of the small sizes of the subsets in the other interventional trials (table 1).[7-15] During the later stent era the Arterial

Table 1. Subsets of patients with diabetes in the major interventional trials

	Total number of patients	Number of diabetics	Recruitment period	CABG superior to PCI in diabetics at primary end point
BARI[7,10]	1,829	353	1988–1991	Yes
CABRI[9]	1,054	122	1988–1992	No
EAST[11]	392	59	1987–1990	No (yes after seven years)
RITA[8]	1,011	62	1988–1991	No
ERACI[13]	127	13	1988–1990	No
GABI[12]	359	43	1986–1991	No
ARTS[14]	1,205	208	1996–1997	No
ERACI II[15]	450	77	1996–1998	No

Revascularisation Therapy Study (ARTS) trial addressed the issue of multivessel stenting versus surgery; there was no difference in the primary end point of death/MI/CVA between PCI and CABG in terms of the general population of patients but there was a trend in favour of surgery in the diabetic subset.[14]

Diabetic patients should be considered as a separate population

Diabetics have a higher frequency of associated risk factors, including hypertension and hyperlipidaemia,[16] and they also have risks specific to diabetes largely resulting from insulin resistance, hyperinsulinaemia and hyperglycaemia.[17] These include dyslipidaemia (characterised by increased concentrations of small dense low-density lipoproteins [LDLs], triglyceride-rich very low-density lipoproteins [VLDLs] and low concentrations of high-density lipoproteins [HDLs]); endothelial dysfunction (characterised by increased expressions of plasminogen activator inhibitor (PAI)-1 and cellular adhesion molecules); and impaired vasomotor activity that is related to decreased availability of nitric oxide. Other risk factors include oxidative stress (increased concentrations of markers such as oxidised LDLs and F2-isoprostanes), inflammation (resulting in increased expression of markers such as fibrinogen and C-reactive protein [CRP]), abnormalities in coagulation and fibrinolysis (resulting in overproduction of fibrinogen and expression of PAI-1 and tissue plasminogen activator [t-PA]), and glycation of proteins (resulting in the formation of advanced end products [AGE] in LDL and collagen within the arterial wall, which have a variety of proatherogenic effects).

Diabetic coronary heart disease is different

These patients have a greater need for vascularisation and for further revascularisation after their initial procedure.

In addition to the increased risk associated with diabetes, there is evidence that the manifestations of CHD are more severe in diabetics. An analysis of baseline characteristics in BARI of diabetics versus non-diabetics showed that diabetics had a higher incidence of triple vessel disease (46% *vs.* 40% respectively, p=0.05) and left ventricular dysfunction, defined as an ejection fraction below 50% (20% *vs.* 31%, p=0.001).[7] This translated into a significantly lower five-year survival for diabetics.

Likewise, in the angioplasty substudy of the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO IIb),[18] 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 six months (18.8% *vs.* 11.4%, p=0.0001).[19] These differences in clinical features of CHD are reflected in angiographic findings. Typically diabetic patients show diffuse coronary stenoses whereas in non-diabetics stenoses tend to be more localised. The topic of revascularisation in diabetes therefore deserves separate consideration.

Do we need another trial?

While both CABG and PCI have advanced technically in recent years, the field of coronary angioplasty in its routine practice has changed more substantially than has CABG, although the advent of minimally invasive coronary artery surgery and greater use of arterial conduits are clearly relevant.

The Stent Restenosis Study (STRESS)[20] and the BElgian NEtherlands STENT study (Benestent)[21] demonstrated that in selected patients coronary stents reduce the risk of restenosis and subsequent clinical events, a reduction most marked in diabetic patients.[22] New pharmacological interventions, such as glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors and clopidogrel, also appear to improve the results of PCI: importantly, diabetics appear to derive particular benefit.[23-25] Several trials have shown that abciximab and other GPIIb/IIIa inhibitors improve acute outcome and that benefit may be sustained in the long term.[26-28] The combination of stents and GPIIb/IIIa inhibitors appears to be particularly beneficial.[23]

The role of adjunctive peri-procedural pharmocotherapy has been examined in several trials, including the Evaluation of c7E3 for the Prevention of Ischaemic Complications (EPIC) trial, the Evaluation in PTCA to Improve Long-term Outcome with abciximab GPIIb/IIIa blockade (EPILOG) trial and the Evaluation of Platelet IIb/IIIa Inhibitor for STENTing trial (EPISTENT).[23,28,29] In the EPISTENT study, the composite of death, myocardial infarction or target vessel revascularisation at six

months was reduced from 25% to 13% (a 48% reduction, p=0.005) in diabetics treated with abciximab and stenting as opposed to stenting alone.[30] The synergistic efficacy of stenting and abciximab for eligible diabetics undergoing PCI persisted at one-year follow-up. The combined death and MI rate was reduced from 16.3% to 6.8% at one year in diabetic patients treated with abciximab compared to placebo, with cardiac event rates reduced to the level seen in non-diabetic patients.[31] A pooled analysis of three abciximab trials (EPIC, EPILOG and EPISTENT) demonstrated that abciximab decreased the one-year mortality in diabetics from 4.5% to 2.5% (p=0.031) and in non-diabetic patients from 2.6% to 1.9% (p=0.1).[32]

The potential role of the other GPIIb/IIIa inhibitors used in PCI, namely eptifibatide and tirofiban, remains to be determined in diabetics, but the combined use of abciximab and stents in diabetics appears to reduce the level of risk that diabetics have when undergoing PCI. Whether the results achievable with this regimen are comparable to those achieved with modern coronary artery bypass grafting can only be answered by a prospective randomised trial.

The main limitation of PCI has always been in-stent restenosis and a subsequent requirement for further revascularisation 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 is intimated by the recently published Randomised study with the sirolimus-coated Bx Velocity balloon-Expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL) trial, suggesting that the use of rapamycin-coated stents during PCI can reduce or even prevent restenosis.[33] Although these results currently relate only to single vessel angioplasty and follow-up is relatively short (12 months), the potential clinical impact of these coated stents to reduce restenosis is highly likely to be significant. The CARDia trial is well suited to assess this impact (being designed specifically to take account of emergent technologies), and has been modified to facilitate further evaluation of this important new technology.

Value of the study

Diabetics will comprise a third of revascularisations in the next few years, becoming an increasingly important group in cardiology practice. The recent centrally funded health campaign to raise awareness of diabetes in the community is indicative of the concern at all levels of health care provision in the UK about the considerable disease burden conferred by diabetes, with coronary heart disease being the major cause of premature death. There is currently little information available on the value of revascularisation in these patients and how it should best be performed. This has an adverse impact on the patients as individuals, and does not allow appropriate allocation of resources for the future.

The proposed investigation will answer an important clinical question and, crucially, will provide health care planners with hard data to facilitate and promote equity of health care provision, an integral part of the National Service Framework for CHD. It is widely acknowledged that the UK has a particular short-term problem in the provision of CABG, whilst PCI is more readily available. Were PCI and CABG shown to be of comparable benefit in diabetics, this would have an immediate positive impact on waiting times for revascularisation.

The results of this trial will be immediately relevant to the daily work of cardiologists and cardiac surgeons in the UK, translating into improved outcomes and better, evidence-based treatments for highly vulnerable diabetics with life-threatening coronary artery disease. It is the only trial of its type being conducted worldwide and is the first time that a major interventional trial has been conducted in the UK without international parallels. It therefore occupies a unique and important position in the development of interventional cardiology in this country.

Akhil Kapur
Specialist Registrar in Cardiology
Kevin J Beatt
Consultant Cardiologist
Hammersmith Hospital
Du Cane Road, London, W12 OHS.
Correspondence to: Dr K Beatt
(email: k.beatt@ic.ac.uk)

Br J Cardiol (Acute Interv Cardiol) 2003;**10**:AIC 37–AIC 40

References

1. www.who.int/int-pr-1998/en/pr98-63. html. Accessed 01/04/03.
2. Department of Health. Annual report of the chief medical officer. London: Department of Health, 1997. See www.doh.gov.uk/cmo
3. Hauner H. Occurrence of diabetes mellitus in Germany. *Dtsch Med Wochenschr* 1998;**123**:777-82.
4. Pan WH, Cedres LB, Liu K *et al*. Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. *Am J Epidemiol* 1986;**123**:504-16.
5. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;**16**:434-44.
6. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. *Circulation* 1979;**59**:8-13.
7. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI) study. *Circulation* 1997;**96**:1761-9.
8. Coronary angioplasty versus coronary artery bypass surgery: the Randomised Intervention Treatment of Angina (RITA) trial. *Lancet* 1993;**341**:573-80.
9. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). CABRI Trial Participants. *Lancet* 1995;**346**: 1179-84.
10. Comparison of coronary bypass surgery with angioplasty in patients with

multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med* 1996;**335**:217-25.
11. King SB, III, Lembo NJ, Weintraub WS, Kosinski AS, Barnhart HX, Kutner MH. Emory Angioplasty Versus Surgery Trial (EAST): design, recruitment, and baseline description of patients. *Am J Cardiol* 1995;**75**:42C-59C.
12. Hamm CW, Reimers J, Ischinger T, Rupprecht HJ, Berger J, Bleifeld W. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). *N Engl J Med* 1994;**331**: 1037-43.
13. Rodriguez A, Mele E, Peyregne E *et al*. Three-year follow-up of the Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI). *J Am Coll Cardiol* 1996;**27**:1178-84.
14. Serruys PW, Unger F, Sousa JE *et al*. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;**344**:1117-24.
15. Argentine Randomised Trial of Coronary angioplasty with stenting in coronary artery bypass surgery in patients with multi-vessel disease (ERACI II). Rodriguez A. Presented at AHA meeting, Atlanta, Georgia, November 1999. See www.acc.org/education/online/trials/aha99/eraci11.htm
16. Claudi T, Midthjell K, Holmen J, Fougner K, Kruger O, Wiseth R. Cardiovascular disease and risk factors in persons with type 2 diabetes diagnosed in a large population screening: the Nord-Trondelag Diabetes Study, Norway. *J Intern Med* 2000;**248**:492-500.
17. Hayden JM, Reaven PD. Cardiovascular disease in diabetes mellitus type 2: a potential role for novel cardiovascular risk factors. *Curr Opin Lipidol* 2000; **11**:519-28.
18. Hasdai D, Granger CB, Srivatsa SS *et al*. Diabetes mellitus and outcome after primary coronary angioplasty for acute myocardial infarction: lessons from the GUSTO-IIb Angioplasty Substudy. Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes. *J Am Coll Cardiol* 2000;**35**:1502-12.
19. McGuire DK, Emanuelsson H, Granger CB *et al*. Influence of diabetes mellitus on clinical outcomes across the spectrum of acute coronary syndromes. Findings from the GUSTO-IIb study. GUSTO IIb Investigators. *Eur Heart J* 2000;**21**:1750-8.
20. George CJ, Baim DS, Brinker JA *et al*. One-year follow-up of the Stent Restenosis (STRESS I) Study. *Am J Cardiol* 1998;**81**:860-5.
21. Serruys PW, de Jaegere P, Kiemeneij F *et al*. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994;**331**: 489-95.
22. Van Belle E, Bauters C, Leclercq J. Restenosis rates in diabetic patients: A comparison of coronary stenting and balloon angioplasty in native coronary vessels. *Circulation* 1997;**96**:1454-60.
23. EPISTENT investigators. Randomised placebo-controlled and balloon angioplasty controlled trial to assess safety of coronary stenting with use of platelet glycoprotein IIb/IIIa blockade. *Lancet* 1998;**352**:87-92.
24. Pitt B, Waters D, Brown WV *et al*. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularisation Treatment Investigators. *N Engl J Med* 1999;**341**:70-6.
25. Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. *Circulation* 2001;**103**:363-8.
26. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. The ESPRIT Investigators. Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy. *Lancet* 2000;**356**:2037-44.
27. Antman EM, Giugliano RP, Gibson CM *et al*. Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. The TIMI 14 Investigators. *Circulation* 1999;**99**:2720-32.
28. EPIC investigators. Use of monoclonal antibody directed against the platelet IIb/IIIa receptor in high risk coronary angioplasty. *N Engl J Med* 1994;**330**:956-61.
29. Kleiman NS, Lincoff AM, Kereiakes DJ *et al*. Diabetes mellitus, glycoprotein IIb/IIIa blockade, and heparin: evidence for a complex interaction in a multicenter trial. EPILOG Investigators. *Circulation* 1998;**97**:1912-20.
30. Lincoff AM, Califf RM, Moliterno DJ *et al*. Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators. *N Engl J Med* 1999;**341**:319-27.
31. Marso SP, Lincoff AM, Ellis SG *et al*. Optimising the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT (Evaluation of platelet IIb/IIIa inhibitor for stenting trial) diabetic substudy. *Circulation* 1999;**100**:2477-84.
32. Bhatt DL, Marso SP, Lincoff AM, Wolski KE, Ellis SG, Topol EJ. Abciximab reduces mortality in diabetics following percutaneous coronary intervention. *J Am Coll Cardiol* 2000;**35**:922-8.
33. Morice MC, Serruys PW, Sousa JE *et al*. A randomised comparison of a sirolimus-eluting stent with a standard stent for coronary revascularisation. *N Engl J Med* 2002;**346**:1773-80.