

## CLINICAL RESEARCH

## Clinical Trials

# Randomized Comparison of Percutaneous Coronary Intervention With Coronary Artery Bypass Grafting in Diabetic Patients

## 1-Year Results of the CARDia (Coronary Artery Revascularization in Diabetes) Trial

Akhil Kapur, MBChB, MD,\* Roger J. Hall, MD,†‡ Iqbal S. Malik, MMBC<sub>HIR</sub>, PhD,† Ayesha C. Qureshi, MBBS,\* Jeremy Butts, MBBS,† Mark de Belder, MD,§ Andreas Baumbach, MS,|| Gianni Angelini, MD, MCh,|| Adam de Belder, MBBS, MD,¶ Keith G. Oldroyd, MBChB, MD,# Marcus Flather, MBBS,†\*\* Michael Roughton, MSc,\*\* Petros Nihoyannopoulos, MD,† Jens Peder Bagger, MBBS, DSc,† Kenneth Morgan, MBChB, BSc,† Kevin J. Beatt, MBBS, PhD††  
*London, Norwich, Middlesbrough, Bristol, and Brighton, England; and Glasgow, Scotland*

- Objectives** The purpose of this study was to compare the safety and efficacy of percutaneous coronary intervention (PCI) with stenting against coronary artery bypass grafting (CABG) in patients with diabetes and symptomatic multivessel coronary artery disease.
- Background** CABG is the established method of revascularization in patients with diabetes and multivessel coronary disease, but with advances in PCI, there is uncertainty whether CABG remains the preferred method of revascularization.
- Methods** The primary outcome was a composite of all-cause mortality, myocardial infarction (MI), and stroke, and the main secondary outcome included the addition of repeat revascularization to the primary outcome events. A total of 510 diabetic patients with multivessel or complex single-vessel coronary disease from 24 centers were randomized to PCI plus stenting (and routine abciximab) or CABG. The primary comparison used a noninferiority method with the upper boundary of the 95% confidence interval (CI) not to exceed 1.3 to declare PCI noninferior. Bare-metal stents were used initially, but a switch to Cypher (sirolimus drug-eluting) stents (Cordis, Johnson & Johnson, Bridgewater, New Jersey) was made when these became available.
- Results** At 1 year of follow-up, the composite rate of death, MI, and stroke was 10.5% in the CABG group and 13.0% in the PCI group (hazard ratio [HR]: 1.25, 95% CI: 0.75 to 2.09;  $p = 0.39$ ), all-cause mortality rates were 3.2% and 3.2%, and the rates of death, MI, stroke, or repeat revascularization were 11.3% and 19.3% (HR: 1.77, 95% CI: 1.11 to 2.82;  $p = 0.02$ ), respectively. When the patients who underwent CABG were compared with the subset of patients who received drug-eluting stents (69% of patients), the primary outcome rates were 12.4% and 11.6% (HR: 0.93, 95% CI: 0.51 to 1.71;  $p = 0.82$ ), respectively.
- Conclusions** The CARDia (Coronary Artery Revascularization in Diabetes) trial is the first randomized trial of coronary revascularization in diabetic patients, but the 1-year results did not show that PCI is noninferior to CABG. However, the CARDia trial did show that multivessel PCI is feasible in patients with diabetes, but longer-term follow-up and data from other trials will be needed to provide a more precise comparison of the efficacy of these 2 revascularization strategies. (The Coronary Artery Revascularisation in Diabetes trial; [ISRCTN19872154](https://doi.org/10.1185/0954579409031111)) (J Am Coll Cardiol 2010;55:432–40) © 2010 by the American College of Cardiology Foundation

From the \*London Chest Hospital, Barts and The London NHS Trust, London, England; †Imperial College Healthcare NHS Trust, London, England; ‡Norfolk and Norwich University Hospitals, Norwich, England; §James Cook University Hospital, Middlesbrough, England; ||Bristol Heart Institute, Bristol, England; ¶Royal Sussex County Hospital, Brighton, England; #Western Infirmary, Glasgow, Scotland; \*\*Royal Brompton and Harefield NHS Foundation Trust, London, England; and the ††Mayday University Hospital, London, England. Funding for this study was provided by unrestricted research grants from Eli Lilly, Cordis Johnson & Johnson, Bristol-Myers Squibb, Sanofi-Aventis, and the Hammersmith Hospitals Special Trustees. Further

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Diabetic patients make up at least one-fourth of all patients referred for revascularization (1). Their risk of complications from all types of revascularization procedures are higher than that in patients without diabetes, and their long-term prognosis is worse (2–8). The pattern of coronary artery disease in diabetic patients is often complex, with multiple lesions and widespread disease (9), making effective revascularization difficult.

The BARI (Bypass Angioplasty Revascularization Investigation) compared percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) in patients with multivessel disease, with a primary end point of mortality at 5 years (10). The analysis of the subset of 353 diabetic patients showed that after 5 years of follow-up, patients initially treated with PCI had double the mortality of those randomized to CABG (11). CABG was already established as the standard revascularization strategy in nondiabetic patients with left main stem coronary artery disease or 3-vessel coronary disease and impaired LV function, and the BARI subgroup results led to this being extended to all patients with diabetes and multivessel disease. However, the BARI was conducted before bare-metal stents (BMS) and glycoprotein IIb/IIIa inhibitors were available. In addition, PCI has evolved further with the introduction of drug-eluting stents (DES) and new oral antiplatelet strategies (12–15). There have also been developments in surgery, including increased arterial revascularization and off-pump techniques, but their impact on outcome has been less dramatic (16–18). In the context of the continuing refinement in treatment strategies and an increase in the number of diabetic patients requiring revascularization, there is a need to continually assess the role of contemporary PCI compared with CABG. Accordingly, the CARDia (Coronary Artery Revascularization in Diabetes) trial was undertaken to compare PCI plus stenting with CABG in patients with diabetes and multivessel coronary artery disease (19).

## Methods

The trial design and study protocol were described previously (19). In brief, patients were considered eligible if they had diabetes and either multivessel coronary disease or complex single-vessel disease (ostial or proximal left anterior descending artery disease) and were recommended to have coronary revascularization on clinical grounds. After review of each case by an experienced interventional cardiologist and cardiac surgeon, there had to be agreement that there was reasonable equipoise in the risks and benefits of PCI and CABG before a patient could be randomized. The exclusion criteria were the inability to consent, age older than 80 years, previous revascularization, left main stem disease, cardiogenic shock, recent ST-segment elevation myocardial infarction (MI) (within 6 weeks), known ejection fraction <20%, and contraindications to antiplatelet therapy. National and institutional ethical approval was

obtained for all 24 participating centers in the United Kingdom (n = 22) and Ireland (n = 2) (Online Appendix). All patients gave written informed consent before randomization. Randomization was undertaken, by either a local secure computer-based system or telephone contact with the coordinating center stratifying for urgency of intervention (acute/elective), sex, and number of diseased vessels (3/<3). Confirmation of eligibility criteria was required before release of randomization allocation. Center-

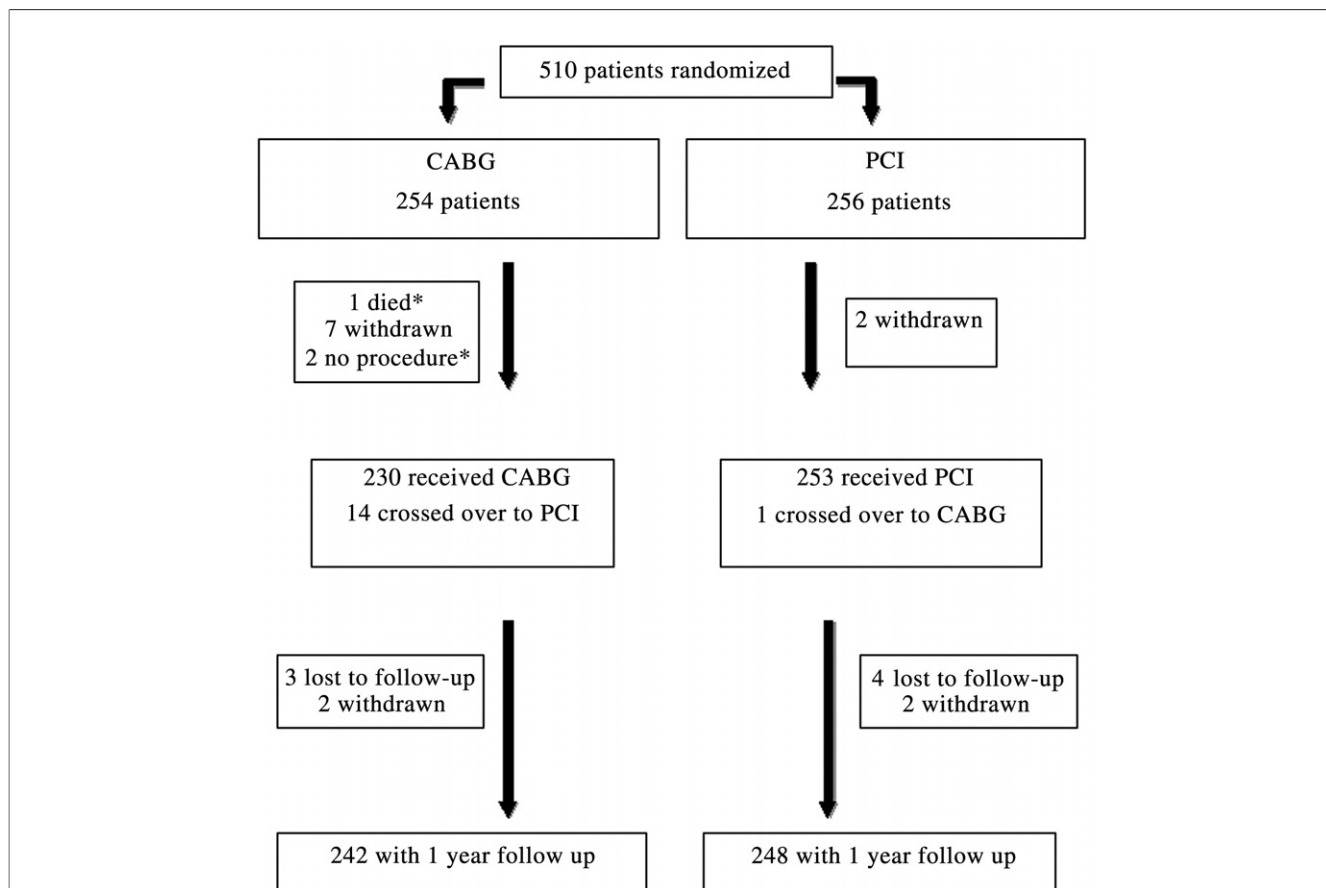
specific randomization was undertaken with stratification according to sex, number of diseased vessels, and whether the procedure was urgent or elective. Operators in both treatment arms were encouraged to perform as complete a revascularization as possible. Staged procedures were allowed and included as part of the index revascularization if the operator decided this before the end of the initial procedure. Contemporary techniques, such as arterial revascularization and off-pump procedures, were encouraged in patients randomized to CABG. The PCI strategy included the unrestricted use of stents and routine administration of abciximab. The trial was started using BMS, but when they became available, patients received DES (Cypher stents, Cordis, Johnson & Johnson, Bridgewater, New Jersey). The protocol recommendation for clopidogrel use after PCI was 1 to 3 months after BMS placement and 12 months after DES placement. The primary end point was a composite of death, MI, and stroke assessed at 1 year after randomization with a major secondary end point of repeat revascularization also assessed at 1 year. With the advent of troponin, the definition of MI was amended, and this together with the definitions of the trial end points are summarized (Online Appendix). The reporting of a serious adverse event was based on notification by the local investigator and in the case of MI did not depend on routine biomarker assessment post-procedure.

**Outcomes and follow-up.** All major events including death, MI, stroke, bleeding, and repeat revascularization were reviewed by the Critical Events Adjudication Committee, which consisted of cardiologists and surgeons who were blinded to treatment allocation. There were 2 adjudicators for each event, with a third used if required. An independent Data and Safety Monitoring Board comprising 2 cardiologists and 1 surgeon reviewed trial data according to protocol.

**Statistical methods.** All analyses were performed using the intent-to-treat principle. The primary outcome was the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 1 year (time to first event). Additional outcomes of interest were the individual elements of the composite outcome, repeat revascularization, bleeding, angina classifi-

## Abbreviations and Acronyms

<b>BMS</b>	= bare-metal stent(s)
<b>CABG</b>	= coronary artery bypass grafting
<b>CI</b>	= confidence interval
<b>DES</b>	= drug-eluting stent(s)
<b>HR</b>	= hazard ratio
<b>MACCE</b>	= major adverse coronary and cerebral events
<b>MI</b>	= myocardial infarction
<b>PCI</b>	= percutaneous coronary intervention



**Figure 1** Patient Enrollment and Follow-Up

\*These patients are included in the 1-year follow-up. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

ation, and the composite of the primary outcome and repeat revascularization (major adverse coronary and cerebral events [MACCE]). Timing of follow-up was taken from the date of randomization, with all patients being censored at their last observed follow-up time, or 365 days if their last observed follow-up time was >1 year. A Cox proportional hazards model was used to compare the survival times in the 2 treatment arms, and the survival distributions were constructed using the Kaplan-Meier method. Results of the survival analysis are presented as unadjusted hazard ratio (HR) and 95% confidence interval (CI). Variables are summarized using mean (SD) or number (%), as appropriate. Comparisons of continuous variables were made using *t* tests, and the chi-square test was used to compare categorical variables. All analyses were performed using Stata 10.1 (StataCorp, College Station, Texas), and a *p* value <0.05 was considered to be statistically significant. Pre-specified subgroups included 3-vessel/2-vessel disease, BMS or DES, insulin/no insulin treatment, sex, age (younger than 65/65 years and older). For the BMS/DES subgroup, PCI patients were compared with concurrent CABG controls using the date that the DES was first introduced as the cut point (excluding the few patients who

received only BMS after this date). The *p* values for interaction in these subgroups (i.e., whether there seems to be a difference in treatment effect in the strata of the subgroup) are provided.

**Sample size estimate.** CABG has historically been assumed to be superior to PCI in patients with diabetes and multivessel disease. The sample size was calculated at 600 patients, based on event rates in the ARTS (Arterial Revascularization Therapy Study) (6), the meta-analysis of the EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications), EPILOG (Evaluation in PCTA to Improve the Long-Term Outcome With Abciximab GP IIb/IIIa), and EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting) trials (20) as well as the ability to enroll this number over approximately 3 years. We used an exploratory noninferiority design model (21). The most favorable assumption was that the composite of death, MI, and stroke would occur at a rate of 9.0% in the PCI arm and at 12.5% in the surgical arm, suggesting that an odds ratio of 0.69 in favor of PCI (with upper CI boundary of 1.3) would allow us to declare PCI as noninferior. We recognized that the study could be underpowered for clinical outcomes, but would have reasonable power (approximately

**Table 1** Baseline Clinical Characteristics of CARDia Trial Patients

Variable	Total (n = 510)	CABG (n = 254)	PCI (n = 256)
Age (yrs), mean (SD)	510	63.6 (9.1)	64.3 (8.5)
Male, n (%)	509	197 (77.9)	181 (70.7)
Systolic blood pressure (mm Hg), mean (SD)	434	137.3 (18.7)	136.7 (20.8)
Diastolic blood pressure (mm Hg), mean (SD)	434	73.3 (12.0)	73.6 (10.6)
Heart rate (beats/min), mean (SD)	431	69.9 (13.2)	68.7 (12.9)
Body mass index (kg/m <sup>2</sup> ), mean (SD)	486	29.4 (5.3)	29.2 (4.9)
Ethnicity, n (%)	505		
White		181 (72.4)	171 (67.1)
Asian		52 (20.1)	66 (25.9)
Black		6 (2.4)	6 (2.4)
Other		11 (4.4)	12 (4.7)
Admission type, n (%)	510		
Acute		60 (23.6)	55 (21.5)
Elective		194 (76.4)	201 (78.5)
Diabetes status	510		
Type 1, n (%)		17 (6.7)	8 (3.1)
Noninsulin treated, n (%)		155 (60.9)	168 (65.5)
Insulin treated, n (%)		99 (39.1)	88 (36.5)
Years with diabetes, mean (SD)	477	10.4 (9.6)	10.1 (9.6)
Smoking status, n (%)	510		
Nonsmoker		161 (63.4)	162 (63.3)
Ex-smoker		15 (5.9)	12 (4.7)
Smoker		59 (23.2)	63 (24.6)
Unknown		19 (7.5)	7 (2.4)
Diseased vessels, n (%)	510		
3-vessel disease		149 (59.7)	166 (64.8)
2-vessel disease		88 (34.7)	72 (28.1)
Bifurcation		5 (2.0)	2 (0.8)
Proximal LAD		12 (4.7)	16 (6.3)
Hypertension, n (%)	508	203 (80.6)	196 (76.6)
Hyperlipidemia, n (%)	507	220 (87.3)	237 (92.9)
History of renal impairment, n (%)	508	10 (4.0)	14 (5.5)
Peripheral vascular disease, n (%)	508	13 (5.2)	6 (2.4)
COPD, n (%)	446	24 (9.5)	24 (9.4)
Cerebrovascular disease history (stroke or TIA), n (%)	508	12 (5.6)	8 (3.5)
Left ventricular function, n (%)*	329		
Normal or good		106 (59.3)	98 (55.4)
Mild impairment		37 (24.3)	43 (24.3)
Moderate impairment		23 (15.1)	34 (19.2)
Severe impairment		2 (1.3)	2 (1.1)
Ejection fraction (%), mean (SD)	256	60.0 (12.7)	59.1 (14.4)
Creatinine (μmol/l), mean (SD)	431	107.0 (70.7)	104.2 (50.2)
Cholesterol (mmol/l), mean (SD)	372	3.85 (0.94)	4.05 (1.05)
LDL (mmol/l), mean (SD)	244	1.94 (0.69)	2.13 (0.84)
HDL (mmol/l), mean (SD)	292	1.17 (0.57)	1.17 (0.49)
Triglyceride (mmol/l), mean (SD)	320	1.88 (1.11)	1.84 (1.04)

\*Assessed using a qualitative scale from the angiogram.

CABG = coronary artery bypass grafting; CARDia = Coronary Artery Revascularization in Diabetes; COPD = chronic obstructive pulmonary disease; HDL = high-density lipoprotein; LAD = left anterior descending artery; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

80% power at alpha = 0.05) to detect differences in the composite of death, stroke, MI, or repeat revascularization, which is the MACCE outcome used in the ARTS 1 (6). Thus, the sample size was a pragmatic one based on projected enrollment rates.

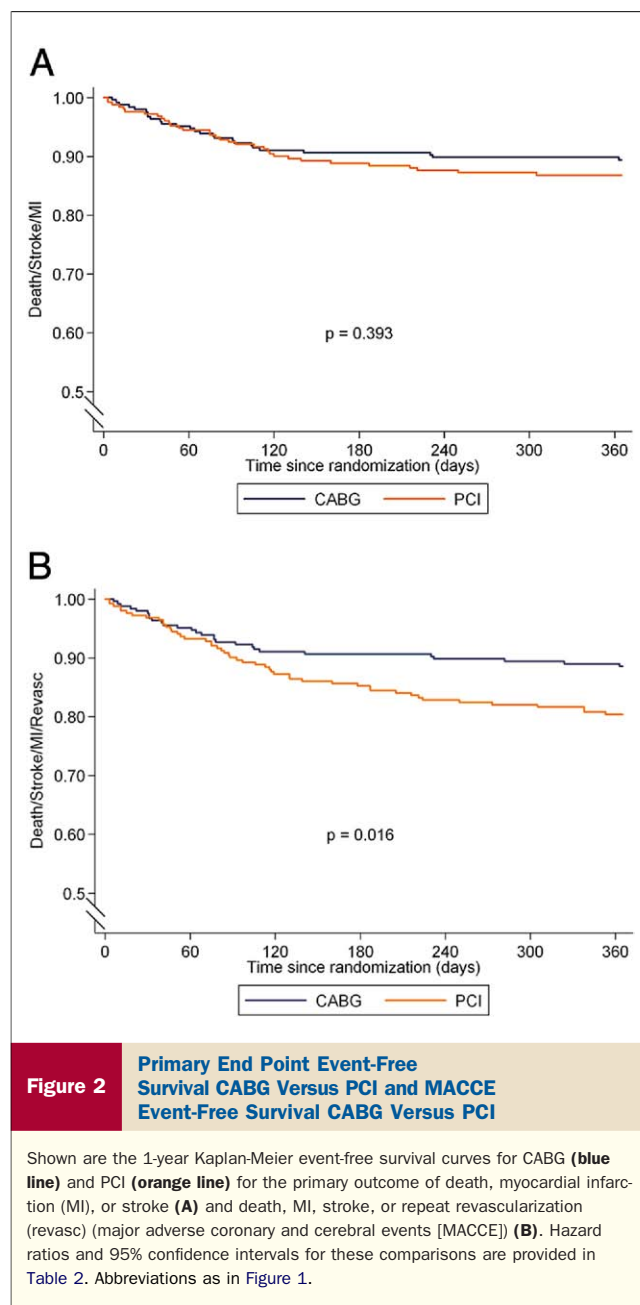
## Results

The trial enrolled 510 patients (254 were randomized to CABG and 256 to PCI) from January 2002 to May 2007. The median follow-up was 365 days. In the CABG group,

230 of 254 patients (91%) actually underwent CABG, with 1 patient dying before the operation and 14 crossing over to PCI. In the PCI group, 253 of 256 patients (99%) actually underwent PCI, and 1 patient crossed over to CABG (Fig. 1). Baseline clinical characteristics were well matched, and the number of diseased vessels, baseline creatinine, and left ventricular function were also similar between the 2 groups (Table 1). Thirty-eight percent of patients were treated with insulin, and 5% of all patients had type 1 diabetes. The duration of diabetes before randomization for each group was 10 years, and the baseline glycosylated hemoglobin was 7.9% in both groups. It was a protocol requirement that all patients in both groups had aggressive diabetic control post-randomization with a target glycosylated hemoglobin of <7%. However, this target was not achieved, and it remained 7.9% in the CABG group and 7.7% in the PCI group at the 1 year follow-up ( $p = 0.086$ ).

The time from randomization to procedure was a median of 64 days for CABG and 38 days for PCI ( $p < 0.001$ ). This reflected the relatively long waiting times in the United Kingdom during the course of this study. The time spent in hospital was a median of 9 days for surgery and 1 day for angioplasty ( $p < 0.001$ ). In the PCI group before the procedure, 100% of patients took aspirin, 95% clopidogrel, and 95% abciximab. Sixty-five percent of patients had 3-vessel disease, of whom 88% had complete revascularization and only 2.6% had staged procedures. On average, 3.6 stents (a mean total stent length of 71 mm) were implanted per patient. Cypher stents were used in 69% of patients and BMS in 31%. Fifteen patients received both DES and BMS and were included in the DES subgroup. In the CABG group, 60% of patients had 3-vessel disease, of whom 90% underwent complete revascularization. On average, 2.9 grafts were used per patient. Ninety-four percent of patients underwent a left internal mammary artery graft and 17% at least 2 arterial grafts, and 31% underwent off-pump surgery.

The combined rate of death, MI, and stroke in the CABG group was 10.5% compared with 13.0% in the PCI group (HR: 1.25, 95% CI: 0.75 to 2.09) (Fig. 2A). The noninferiority margin of 1.3 was exceeded by the upper limit of the CI for the primary end point, indicating that our results could not demonstrate that PCI is noninferior to CABG. Subsequent comparisons are all provided using conventional comparative methods. The all-cause mortality rate in the CABG group was 3.2% and 3.2% in the PCI group ( $p = 0.97$ ; HR: 0.98, 95% CI: 0.37 to 2.61) with repeat revascularization rates of 2.0% and 11.8% ( $p < 0.001$ , HR: 5.31, 95% CI: 2.0 to 14.11), respectively. The composite of MACCE combining repeat revascularization with the primary end point was 11.3 versus 19.3%, ( $p = 0.016$ ; HR: 1.77; 95% CI: 1.11 to 2.82) in the CABG and PCI groups, respectively (Fig. 2B). The occurrence rate of Thrombolysis In Myocardial Infarction (TIMI) major bleeding at 1 year in the CABG group compared with the PCI group was 6.1% versus 1.2% ( $p = 0.009$ ; HR: 0.19,



95% CI: 0.06 to 0.67), respectively. Peri-procedural MI rates were similar in the 2 groups, but the rate of late MI occurring >7 days after the index revascularization procedure was higher in the PCI arm ( $p = 0.016$ ) (Table 2).

Initially, BMS were used in the CARDia trial, but subsequently DES became available and were used routinely. We compared outcomes for PCI patients undergoing DES placement with CABG patients enrolled during the same time period (and the same for PCI patients undergoing BMS placement). The rates of death, MI, or stroke in this subgroup of CABG versus DES patients ( $n = 350$ ; 69% of the total sample) were 12.4% versus 11.6%, respectively (HR: 0.93; 95% CI: 0.51 to 1.71), and for CABG versus BMS patients ( $n =$

**Table 2 Major End Points at 1 Year**

Adjudicated Events Post-Randomization	CABG (n = 248)	PCI (n = 254)	PCI vs. CABG	
			HR (95% CI)	p Value
Death	8 (3.2)	8 (3.2)	0.98 (0.37-2.61)	0.97
Nonfatal MI (total)	14 (5.7)	25 (9.8)	1.77 (0.92-3.40)	0.088
Periprocedural MI	11 (4.4)	12 (4.7)	1.08 (0.47-2.44)	0.819
Late MI*	3 (1.2)	14 (5.5)	4.64 (1.33-16.16)	0.016
Nonfatal stroke	7 (2.8)	1 (0.4)	0.14 (0.02-1.14)	0.066
Composite outcome of death, nonfatal MI, and nonfatal stroke at 1 year: primary outcome	26 (10.5)	33 (13.0)	1.25 (0.75-2.09)	0.393
Further revascularization at 1 year	5 (2.0)	30 (11.8)	6.18 (2.40-15.94)	<0.001
Composite outcome of death, nonfatal MI, nonfatal stroke, and repeat revascularization at 1 year: secondary outcome	28 (11.3)	49 (19.3)	1.77 (1.11-2.82)	0.016
TIMI major bleed	15 (6.1)	3 (1.2)	0.19 (0.06-0.67)	0.009

Values are n (%). \*Late MI defined as occurring >7 days after index revascularization procedure. (Note: 1 patient in the PCI group had both a periprocedural and a late MI.)  
CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

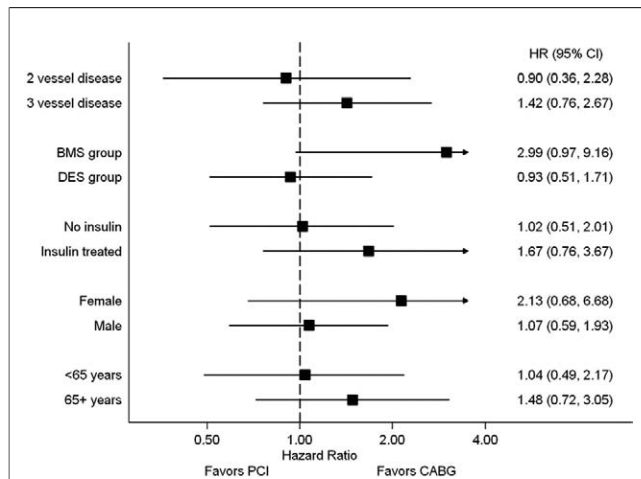
152), they were 5.7% versus 15.9% (HR: 2.99; 95% CI: 0.97 to 9.16; test for interaction p = 0.076) (Table 3, Fig. 3). MACCE rates were 12.9% versus 18.0% (p = 0.14) in the CABG versus DES patients (Table 3). In the subgroup of patients with 3-vessel disease, which accounted for approximately 60% of patients, the composite of death, MI, and stroke occurred in 11.0% versus 15.2%, and for 2-vessel disease patients, the rates were 9.8% versus 8.9%, in CABG and PCI groups respectively (interaction p = 0.4). Full data for the 5 subgroups tested for the primary outcome and for MACCE are shown in Table 3 and Figure 3.

Medication use at 1 year showed some imbalances, with clopidogrel use being higher in the PCI group, as would be expected, whereas more patients were taking insulin in the CABG group at 1 year. Statins and aspirin were used in approximately 85% in both groups at 1 year (Table 4). A comparison of CABG and PCI at baseline showed that Canadian Cardiovascular Society class was similar in both groups (p = 0.719). After 1 year, symptoms had improved in both groups, but patients randomized to CABG had significantly less angina (p < 0.001) (Table 4).

**Table 3 Outcomes in Subgroups of Interest**

	CABG		PCI		HR	95% CI	Interaction p Value
	Patients	n (%)	Patients	n (%)			
<b>Death, MI, stroke at 1 yr</b>							
2-vessel disease	102	10 (9.8)	90	8 (8.9)	0.9	0.36-2.28	0.419
3-vessel disease	146	16 (11.0)	164	25 (15.2)	1.42	0.76-2.67	
BMS group	70	4 (5.7)	82	13 (15.9)	2.99	0.97-9.16	0.076
DES group	178	22 (12.4)	172	20 (11.6)	0.93	0.51-1.71	
No insulin	151	16 (10.6)	161	17 (10.6)	1.02	0.51-2.01	0.348
Insulin	97	10 (10.3)	92	16 (17.4)	1.67	0.76-3.67	
Female	56	4 (7.1)	74	11 (14.9)	2.13	0.68-6.68	0.289
Male	192	22 (11.5)	180	22 (12.2)	1.07	0.59-1.93	
Age <65 yrs	123	14 (11.4)	119	14 (11.8)	1.04	0.49-2.17	0.497
Age ≥65 yrs	125	12 (9.6)	135	19 (14.1)	1.48	0.72-3.05	
<b>Death, MI, stroke, repeat revascularization (MACCE)</b>							
2-vessel disease	102	10 (9.8)	90	13 (14.4)	1.48	0.65-3.38	0.641
3-vessel disease	146	18 (12.3)	164	36 (22.0)	1.88	1.07-3.31	
BMS group	70	5 (7.1)	82	18 (22.0)	3.42	1.27-9.22	0.131
DES group	178	23 (12.9)	172	31 (18.0)	1.41	0.82-2.42	
No insulin	151	18 (11.9)	161	26 (16.2)	1.41	0.77-2.58	0.243
Insulin	97	10 (10.3)	92	23 (25.0)	2.47	1.18-5.2	
Female	56	5 (8.9)	74	15 (20.3)	2.4	0.87-6.61	0.489
Male	192	23 (12.0)	180	34 (18.9)	1.62	0.95-2.74	
Age <65 yrs	123	14 (11.4)	119	21 (17.7)	1.58	0.8-3.1	0.662
Age ≥65 yrs	125	14 (11.2)	135	28 (20.7)	1.94	1.02-3.68	

BMS = bare-metal stent(s); DES = drug-eluting stent(s); MACCE = major adverse coronary and cerebral event; other abbreviations as in Tables 1 and 2.



**Figure 3** Forest Plot of Death, Myocardial Infarction, and Stroke in Key Subgroups

Squares represent point estimates for the hazard ratio (HR) and horizontal lines represent 95% confidence interval (CI). Arrows indicate that the upper limit of HR goes off the log scale. Also see Table 3. BMS = bare-metal stent(s); DES = drug-eluting stent(s); other abbreviations as in Figure 1.

**Discussion**

The CARDia trial is the first prospective randomized trial to evaluate the safety and efficacy of PCI compared with those of CABG in patients with diabetes. There was a nonsignificantly higher rate of the composite of death, MI, and stroke (driven by a higher rate of MI) and significantly higher rates of repeat revascularization in the PCI group. The pre-specified noninferiority margin was not met. Stroke rates showed a trend favoring PCI, and mortality rates were the same in the 2 groups. The trial provides the

largest existing dataset of diabetic patients with complex disease randomized to PCI or CABG.

The event rate in the PCI arm was higher than predicted, likely due to the increased complexity of coronary disease in the CARDia trial compared with previous trials, a trend also seen in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial. The SYNTAX trial using the SYNTAX score as a measure of complexity showed that increased complexity has a disproportionately adverse effect on the outcome of PCI patients compared with CABG patients (22). This largely unforeseen change in practice will need to be taken into consideration when calculating sample sizes for future trials and when applying the result to current clinical practice.

The prevalence of diabetes is increasing, and approximately 8% of adults in developed countries have diabetes (23). Cardiovascular complications remain the leading cause of mortality among patients with type 2 diabetes mellitus, accounting for as many as 80% of deaths (24,25). Although CABG is generally considered a more effective revascularization strategy in patients with diabetes, it also carries a greater morbidity, increased length of hospital stay, and longer recovery times compared with PCI.

The BARI (subjects recruited from 1988 to 1991) first highlighted the difference in mortality rates between CABG and PCI in diabetic patients (11). The ARTS (recruited from 1996 to 1997) showed mortality rates of 3.1% for CABG and 6.3% for PCI at 1 year (6). In the CARDia trial, mortality for the PCI group was 3.2%, which is one-half that seen in the ARTS diabetic subgroup, whereas CABG mortality was the same as in the ARTS at 3.2%. Overall rates of MI in the PCI group were nonsignificantly higher than CABG, and this seems to be driven by a significant

**Table 4** Medications and CCS Class at Baseline and 1 Year

	CABG Baseline (n = 246)	PCI Baseline (n = 252)	CABG at 1 Year (n = 217)	PCI at 1 Year (n = 223)	p Value CABG vs. PCI at 1 Year
<b>Medications and HbA<sub>1c</sub></b>					
Aspirin	208 (82.2)	224 (87.5)	197 (87.2)	191 (83.4)	0.258
Clopidogrel	71 (28.1)	109 (42.8)	23 (10.3)	124 (54.4)	<0.001
Aspirin and clopidogrel	65 (25.7)	101 (39.6)	15 (16.5)	116 (50.9)	<0.001
Statins	134 (53.0)	144 (56.5)	201 (89.3)	191 (83.4)	0.066
ACE inhibitors	207 (81.8)	223 (87.5)	135 (60.3)	128 (56.1)	0.374
Oral hypoglycemics	152 (60.1)	167 (65.5)	138 (61.1)	150 (65.5)	0.326
Insulin	99 (39.1)	93 (36.5)	92(40.9)	68(29.8)	0.014
HbA <sub>1c</sub> , mean (SD)	7.9 (1.6)	7.9 (1.4)	7.9 (1.6)	7.7 (1.4)	0.106
<b>CCS class</b>					
0	38 (15.5)	38 (15.1)	192 (88.5)	159 (71.3)	0.001
I	165 (67.1)	183 (72.6)	16 (7.4)	37 (16.6)	(global p value for all classes of angina)
II	27 (11.0)	19 (7.5)	8 (3.7)	21 (9.4)	
III	12 (4.9)	9 (3.6)	1 (0.5)	2 (0.9)	
IV	1 (0.4)	1 (0.4)	0 (0)	3 (1.4)	
IVa	3 (1.2)	2 (0.8)	0	1 (0.5)	

Values are n (%) unless otherwise indicated. There were no significant differences between groups at baseline. One-year denominators are maximum number available; some groups have smaller denominators due to missing data.

ACE = angiotensin-converting enzyme; CCS = Canadian Cardiovascular Society; HbA<sub>1c</sub> = glycosylated hemoglobin; other abbreviations as in Table 1.

excess in late MIs occurring >7 days after the index procedure. In the ARTS, the rate of revascularization was 22.3% at 1 year in the PCI diabetic subgroup (4.1% for CABG), but in the CARDia trial, the rate was 11.8% (9.4% in those receiving DES), although this was still considerably higher than the CABG revascularization rate of 2.0% ( $p < 0.001$ ) (6). Thus, the improvement over time seems greater in the patients treated with PCI. These improved outcomes are despite the fact that patients recruited in the CARDia trial had more extensive disease. For example, 3-vessel disease accounted for just 36% and 38% of patients in the CABG and PCI diabetic subsets, respectively, in the ARTS compared with 60% and 65% in the CARDia trial (Table 1). On average, 3.0 stents were implanted in the ARTS PCI diabetic subset with an average total stent length per patient of 52 mm. The respective figures for the CARDia trial were 3.6 and 71 mm. The recently reported SYNTAX trial shows a continuation of the trend with figures of 4.6 and 86 mm, respectively, in the study as a whole (22). In the ARTS, MI rates at 1 year were 2.1% in the CABG arm, 6.3% in the PCI arm, and 0.6% in the DES arm (26). The rate of MI in CARDia trial was higher, although this may be related to the MI definition, which has often varied among trials (27,28).

In contrast to these progressive improvements, a finding that has remained largely consistent throughout the landmark revascularization trials has been the higher stroke rate in the CABG arm compared with the PCI arm, particularly for diabetic patients. In the recent SYNTAX trial, stroke rates were 2.2% and 0.6% in the CABG and PCI groups, respectively (22). The higher stroke rate observed in both the CARDia and SYNTAX trials in the surgical arm needs to be taken into consideration when deciding which revascularization procedure is preferred in these patients. A recent individual patient data meta-analysis of all randomized CABG versus PCI trials (including older pre-stent trials) with a total sample size of 7,812 patients has shown that overall mortality rates for a median follow-up of 6 years were approximately 16% in both groups, but mortality (even excluding the BARI) was significantly lower in diabetic patients in the CABG group, and there was also a favorable trend for CABG with older age (29). Because the overall CARDia trial was underpowered, we cannot make any clear statements about the subgroups, even though these are presented (Table 3, Fig. 3); however, there seemed to be a trend suggesting that DES may provide a better outcome than BMS.

**Study limitations.** The CARDia trial was underpowered for the primary composite outcome, but we believe that this outcome was more meaningful and consistent with other major cardiovascular therapy trials, than the conventional MACCE outcome, which is driven by repeat revascularization. Longer-term follow-up will increase power, as has been observed in other trials (11,30). None of the CABG versus PCI trials have been adequately powered for clinical outcomes, and even the pooled analysis of all the random-

ized trials with approximately 7,800 patients has not shown clear differences in mortality between the 2 strategies (29). We achieved 85% of the expected sample, which still represents the largest study of revascularization in diabetic patients. The definition and detection of MI in the CARDia trial can be questioned because central monitoring of markers of myocardial damage was not performed, but, as discussed, there is no consensus on how MI should be detected in a clinical trial setting, and our approach of investigator-reported events with central adjudication remains valid. The type of stent used changed during the trial from BMS to DES, which is a simple reflection of the ever-changing practice in coronary revascularization, and most trials have had changes in practice during the enrollment phase including new balloons, guide catheters, and stents. Although the CARDia trial was a comparison of 2 revascularization strategies, there may be some patients with type 2 diabetes and stable coronary disease who will do equally well with optimal medical therapy, as recently illustrated by BARI in type 2 diabetes (31).

## Conclusions

The 1-year results of the CARDia trial did not demonstrate the noninferiority of PCI versus CABG for revascularization of diabetic patients. However, the results suggest that there could be greater equipoise between the 2 strategies, with the decision to use CABG or PCI being based on information from clinical trials, clinician judgment, and patient preference. Longer-term follow-up of the CARDia trial and data from other ongoing trials such as FREEDOM (Future REvascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) (32) will provide further information on optimal strategies for coronary revascularization in diabetic patients.

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**Reprint requests and correspondence:** Dr. Kevin J. Beatt, Mayday University Hospital, London Road, London CR7 7YE, England. E-mail: [dr.beatt@heartbeatt.com](mailto:dr.beatt@heartbeatt.com).

#### REFERENCES

1. Daemen J, Kuck KH, Macaya C, et al. Multivessel stenting in patients with and without diabetes mellitus: 3-year follow-up of the ARTS-II (Arterial Revascularization Therapies Study-Part II) trial. *J Am Coll Cardiol* 2008;52:1957-67.
2. Stein B, Weintraub WS, Gebhart SP, et al. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. *Circulation* 1995;91:979-89.
3. Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 1996;94:1818-25.
4. Alderman EL, Corley SD, Fisher LD, et al., for the CASS Participating Investigators and Staff. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). *J Am Coll Cardiol* 1993;22:1141-54.
5. Thourani VH, Weintraub WS, Stein B, et al. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. *Ann Thorac Surg* 1999;67:1045-52.
6. Abizaid A, Costa MA, Centemero M, et al. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. *Circulation* 2001;104:533-8.
7. Flaherty JD, Davidson CJ. Diabetes and coronary revascularization. *JAMA* 2005;293:1501-8.
8. Marcheix B, Vanden EF, Demers P, Bouchard D, Cartier R. Influence of diabetes mellitus on long-term survival in systematic off-pump coronary artery bypass surgery. *Ann Thorac Surg* 2008;86:1181-8.
9. Nicholls SJ, Tuzcu EM, Kalidindi S, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. *J Am Coll Cardiol* 2008;52:255-62.
10. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;335:217-25.
11. The BARI Investigators. 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). *Circulation* 1997;96:1761-9.
12. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-80.
13. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-23.
14. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-20.
15. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med* 1994;330:956-61.
16. Acar C, Ramsheyi A, Pagny JY, et al. The radial artery for coronary artery bypass grafting: clinical and angiographic results at five years. *J Thorac Cardiovasc Surg* 1998;116:981-9.
17. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet* 2001;358:870-5.
18. Moller CH, Penninga L, Wetterslev J, Steinbruchel DA, Gluud C. Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: systematic review with meta-analyses and trial sequential analyses. *Eur Heart J* 2008;29:2601-16.
19. Kapur A, Malik IS, Bagger JP, et al. The Coronary Artery Revascularisation in Diabetes (CARDia) trial: background, aims, and design. *Am Heart J* 2005;149:13-9.
20. 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.
21. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Med* 1990;9:1447-54.
22. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-72.
23. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care* 1998;21:518-24.
24. Harris MI. Diabetes in America: epidemiology and scope of the problem. *Diabetes Care* 1998;21 Suppl 3:C11-4.
25. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;241:2035-8.
26. Serruys PW, Ong AT, Morice MC, et al. Arterial Revascularisation Therapies Study Part II: sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *Eurointervention* 2005;1:147-56.
27. SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. *Lancet* 2002;360:965-70.
28. 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.
29. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009;373:1190-7.
30. Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005;366:914-20.
31. Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503-15.
32. Farkouh ME, Dangas G, Leon MB, et al. Design of the Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial. *Am Heart J* 2008;155:215-23.

**Key Words:** coronary revascularization ■ diabetes ■ multivessel disease.

#### APPENDIX

For a list of participating centers, primary end point definitions, and the trial committees, please see the online version of this article.