Myocardial function may improve equally in diabetic patients following both multivessel percutaneous coronary intervention and coronary artery bypass grafting: results from a CARDia trial substudy

Akhil Kapur1*, Ayesha C. Qureshi1, Sean Gallagher1, Malcolm Finlay1, Iqbal S. Malik2, Jamil Mayet2, Michael Roughton3, Kevin J. Beatt4, Roger J. Hall2, and Petros Nihoyannopoulos2

1London Chest Hospital, Barts and the London NHS Trust, Bonner Road, E2 9JX London, UK; 2Imperial College Healthcare NHS Trust, London, UK; 3Clinical Trials and Evaluation Unit, Royal Brompton Hospital, London, UK; and 4Mayday University Hospital, London, UK

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Aims

The CARDia (Coronary Artery Revascularization in Diabetes) trial compared coronary artery bypass grafting (CABG) and optimal percutaneous coronary intervention (PCI) in diabetic patients with multivessel coronary disease. Patients enrolled had symptoms of myocardial ischaemia. As symptom assessment is flawed in diabetic patients, a substudy was undertaken to compare the extent to which these revascularization strategies alter reversible ischaemia.

Methods and results

Seventy-one patients underwent stress echo at baseline and at 6 months. A 17-segment echocardiographic wall motion score index (WMSI) was assigned at baseline \[\text{WMSI(pre)}\] and at 6 months \[\text{WMSI(post)}\]. An overall score defined the difference: \[\text{WMSI(∂)} = \text{WMSI(pre)} - \text{WMSI(post)}\]. Of 71 patients recruited, 42 underwent PCI and 29 CABG. Mean WMSI(pre) in the PCI group was 1.63 and mean WMSI(post) was 1.32. Mean WMSI(pre) in the CABG group was 1.69 and mean WMSI(post) was 1.46. The PCI WMSI(∂) was 0.31 and CABG WMSI(∂) was 0.23 \([\text{P} = 0.8]\). Of 42 PCI patients, 39 demonstrated ischaemia at baseline. At 6 months 31 had improvements in ischaemia (79%), 5 showed no improvement, and 3 ischaemia worsened. Of 29 CABG patients, 23 demonstrated ischaemia at baseline. At 6 months, 20 had improvements in ischaemia (87%), 2 had no improvement, and in 1 ischaemia worsened. No difference was seen in the number of patients with improvements in reversible ischaemia between PCI and CABG \([\text{79 vs. 87%}, (\text{P} = 0.9)]\).

Conclusion

Optimal revascularization in diabetic patients with multivessel disease remains controversial. This subset analysis of the CARDia trial suggests both PCI and CABG achieve similar improvement in reversible ischaemia.

Keywords

Coronary revascularisation • Diabetes • Stress echocardiography

Introduction

In the general population in the USA and Western Europe, \(\sim 8\%\) of adults have diabetes.\(^1\) By 2010, it is projected that 33 million people in Europe will be affected.\(^2\) This is due almost entirely to an increase in type 2 diabetes mellitus (T2DM). These figures are likely to underestimate the size of the problem as it has been estimated that up to one half of patients affected by diabetes in the general population remain undiagnosed.\(^3\)–\(^5\)

Two-thirds of the deaths and a great deal of the morbidity in patients with diabetes are caused by coronary artery disease (CAD).\(^6\)–\(^8\) While the overall age-adjusted mortality rate associated
with CAD has declined over the past 20 years, this trend is less apparent in patients with T2DM.\(^9\)\(^{-11}\)

The outcomes of patients with diabetes following both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are worse in patients with diabetes compared with non-diabetic patients.\(^12\)\(^{-18}\) Until recently, data that are relevant to the current techniques of revascularization are limited.\(^19\) The CARDia (Coronary Artery Revascularization in Diabetes) trial was designed to address this with the hypothesis that optimal PCI, with drug-eluting stents and abciximab, is not inferior to CABG in patients with diabetes and multivessel coronary disease.\(^20\) The main study, although suggesting similar rates for the primary outcome of death, non-fatal myocardial infarction, and stroke, was underpowered to confirm non-inferiority. It has been demonstrated that completeness of revascularization (subject to lesions being significant) is associated with improved outcomes.\(^21\)\(^{-23}\) However, it is not clear whether PCI achieves the same ‘completeness’ of revascularization in functional terms as is seen with CABG. Thus, the aim of this study was to compare the improvements in reversible ischaemia following the two modes of revascularization.

### Methods

A subset of patients from the CARDia trial underwent dobutamine stress echocardiography prior to their index revascularization procedure and at 6 months follow-up in order to determine whether myocardial function had improved.\(^24\)\(^{-25}\) This was undertaken in patients recruited from the Hammersmith Hospital and St Mary’s Hospital. Patients were selected from these two hospitals because of the availability of stress echo. Patients had already been randomized between CABG and PCI in the main study, and the only criterion for inclusion was agreement to participate in the substudy. Ultimately, there was a difference in the number of patients recruited to this substudy from the two revascularization arms, 42 in the PCI group vs. 29 in the CABG group; this is assumed to be due to chance as only the two centres with the largest number of recruited subjects were involved in this substudy.

The trial design and study protocol have been published previously.\(^26\) In brief, patients were considered eligible if they had diabetes and multivessel coronary 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 inability to consent, age ≥80 years, prior revascularization, left main stem disease, cardiogenic shock, recent ST elevation myocardial infarction (within 6 weeks), known ejection fraction <20%, and contraindications to antplatelet therapy. National and institutional ethical approvals were obtained for all 24 participating centres from the UK (n = 22) and Ireland (n = 2). All patients gave written informed consent prior to randomization. Centre-specific randomization was undertaken with stratification according to gender, number of vessels diseased, and whether the procedure was urgent or elective. Operators in both treatment arms were encouraged to perform as complete revascularization as possible. All patients recruited into the main study at St Mary’s and Hammersmith Hospitals were approached for inclusion into this substudy, and ultimate selection was based on patients’ consent and availability of stress echo slots.

A subset of 71 patients underwent dobutamine stress echo with left ventricular (LV) cavity contrast opacification at baseline and at 6 months. The stress echos were reported by two echocardiographers, with extensive experience in this technique. Patients were classified as having either normal left ventricles, reversible ischaemia (with or without impairment of LV function), or impaired LV function without reversible ischaemia. A wall motion score index (WMSI) was assigned to each stress echo at baseline [WMSI(pre)] and at 6 months post-revascularization [WMSI(post)]. These scores were calculated as the sums of the individual segment scores of regional wall motion based on a four grade scale (1–4, where 1 is normal, 2 mildly hypokinetic, 3 severely hypokinetic, and 4 is akinetic) divided by the number of segments. The analysis was based on a 17-segment model of the left ventricle.\(^27\) Ischaemia was defined as stress-induced wall motion abnormalities that were either new, or a worsening of the pre-existing wall motion abnormality, or biphasic response (improvement at low dose followed by deterioration at high dose). Scar was defined as akinetic or dyskinetic myocardium with no thickening. A test was reported as normal if there was no rest or stress wall motion abnormality.\(^28\) Individual patients were then defined as having either an improvement in their reversible ischaemia, no change from normal, no change from previous reversible ischaemia or a worsening of their reversible ischaemia. They were then assigned an overall wall motion score that defined this difference, where WMSI(i) = WMSI(pre) − WMSI(post).

### Statistical analysis

To compare whether there was a significant change in the WMSI in the patients pre- and post-PCI paired t-tests were used. This analysis was also used in the CABG group. A comparison was made of the WMSI(i) in all the patients in the PCI group with all those in the CABG group using unpaired t-tests.

### Results

Baseline characteristics are shown in Table 1 for both groups of patients. This substudy was prespecified in the design paper.\(^26\) The groups appear broadly similar in their baseline characteristics. Only 55% of the patients recruited to the main study at the Hammersmith and St Mary’s Hospitals participated in this substudy, which was lower than was originally intended. There were four main reasons to explain this low inclusion rate in the substudy: (i) a small proportion of patients refused consent to the substudy; (ii) in the vast majority stress, echo could not be undertaken prior to the revascularization procedure for logistical reasons; (iii) a minority of patients did not return for their 6 months stress echo; (iv) in a few patients, the image quality was not sufficient to include these patients for WMSI analysis. LV function was similar in both groups. There was a trend to more three vessel disease in the PCI group (Table 1).

The results are summarized in Table 2. Of the 42 patients treated with PCI, 39 demonstrated ischaemia at baseline. At 6 months follow-up, 31 of these 39 patients had an improvement in ischaemic burden (79%), with 5 showing no improvement in demonstrated ischaemia and 3 having a worsening of their ischaemia. The other three of the 42 PCI patients showed no change from pre-procedure stress echocardiography that showed no reversible ischaemia despite the presence of coronary stenoses.

Of the 29 patients treated with CABG, 23 had demonstrable ischaemia at baseline. Of these 23 patients, 20 had improvement
in ischaemic burden (87%) at 6 months post-procedure, with 2 showing no improvement in demonstrated ischaemia and 1 having a worsening of their ischaemia. The other six of the 29 CABG patients showed no change from normal stress echocardiography pre-procedure, again despite the presence of significant coronary stenoses.

The mean WMSI(pre) in the PCI group was 1.63 and the mean WMSI(post) was 1.32, representing a significant change in the WMSI ($P = 0.0001$). In the CABG group, the mean WMSI(pre) was 1.69 and the mean WMSI(post) was 1.46, which was also a significant difference ($P = 0.0032$). The PCI WMSI($ii$) was 0.31 and CABG WMSI($ii$) was 0.23, which were not significantly different from each other ($P = 0.8$).

The endpoint comprising no improvement or worsening of ischaemia at 6 months was no different in the two arms [21% of patients at 6 months in the PCI group vs. 13% in the CABG group ($P = 0.9$)]. The patients in the PCI group started with a lower overall WSMI(non-significant) and an excess of three vessel coronary disease compared with the CABG group.

### Discussion

Just under 20% of patients undergoing coronary angiography are known to have diabetes, with diabetic patients accounting for over 20% of all revascularization procedures. The outcomes of patients with diabetes following PCI and CABG remain worse
in patients with diabetes. Coronary revascularization in diabetic patients therefore deserves particular consideration. The CARDia trial was designed to address the hypothesis that optimal PCI is not inferior to up to date CABG in diabetic patients with multivessel coronary disease and is the first trial of this nature exclusively in patients with diabetes. At 1 year of follow-up in the main study, the composite rate of death, MI, and stroke was 10.5% in the CABG group vs. 13.0% in the PCI group [hazard ratio (HR) 1.25, 95% confidence intervals (CI) 0.75–2.09; P = 0.39]. All-cause mortality was 3.2 vs. 3.2% (P = 0.97; HR 0.98, 95% CI 0.37–2.61), and the composite of MACCE (Major Adverse Cardiovascular and Cerebrovascular Events), combining repeat revascularization with the primary endpoint, was 11.3 vs. 19.3%, (P = 0.016; HR 1.77, 95% CI 1.11–2.82) in the CABG and PCI groups, respectively. Based on these results, it may be argued that PCI is a feasible alternative to CABG, albeit with a higher repeat revascularization rate. This is supported by the findings of this substudy that PCI may provide an equivalent alternative technique for reducing or eliminating reversible ischaemia at 6 months after revascularization.

The reduction, or even elimination, in reversible ischaemia is thought to be associated with improved prognosis. In the COURAGE nuclear substudy, the reduction in ischaemia achieved by PCI was greatest among patients with moderate to severe ischaemia defined as a perfusion defect of ≥10% of the myocardium. It is generally considered that functional ischaemia tests, such as myocardial perfusion scintigraphy (MPS) or stress echocardiography, predict events if they demonstrate reversible ischaemia. Although not mandated in the trial protocol, it is clear that most of the patients in the CARDia trial had ischaemia on functional testing. This substudy showed that 39 of 42 PCI patients and 23 of 29 CABG patients had positive stress echocardiograms at baseline. The remainder had angiographically confirmed severe coronary disease as assessed by both a cardiologist and a cardiac surgeon in a multidisciplinary discussion, meriting revascularization on prognostic grounds based on data from the CASS trial. Those patients who did not have positive tests at baseline may have had balanced ischaemia due to three vessel disease leading to falsely negative stress echocardiograms or indeed may have had their angiographic stenoses overestimated. It is well documented that angiographic assessment alone can lead to both over- and underestimation of the significance of coronary stenoses when compared with functional assessments.

This substudy of the CARDia trial, although prespecified and in patients randomized to PCI and CABG, was not stratified; so there may be differences between the two groups. However, these results suggest that when reversible ischaemia is present, revascularization with PCI may alleviate reversible ischaemia at a rate similar to CABG. Furthermore, when it does alleviate reversible ischaemia, it does so at least to the same extent. This suggests that PCI can achieve as complete revascularization as CABG if all significant lesions are targeted.

Reduction in ischaemic burden is important because there are data, such as the COURAGE nuclear substudy, suggesting that the lower the burden of residual ischaemia post-revascularization, the lower the associated risk of death or MI. In addition, patients who undergo complete revascularization (defined as the revascularization of all angiographically significant lesions) do better in terms of survival. However, a strategy of targeted revascularization with the aim of treating only lesions that are functionally important may produce similar or even superior outcomes. The functional importance of these lesions is currently assessed by identifying ischaemia with MPS or stress echocardiography and matching the location to the coronary lesions, or alternatively by the use of fractional flow reserve (FFR) during coronary angiography as demonstrated in the FAME study.

The 1005 patient FAME (FFR vs. Angiography Multivessel Evaluation) study was a randomized trial in patients undergoing PCI, which showed that guiding revascularization with FFR achieved better results than using angiography alone and resulted in the use of fewer stents. At 1 year, the event rate—death, MI, CABG, or repeat PCI—was 13.2% in the FFR group vs. 18.4% in the angiography group (P = 0.02). When the components of the composite endpoint were considered separately, death or myocardial infarction again was significantly lower in the FFR group (P = 0.04).

How applicable these results are to patients with diabetes and MVD may become more apparent once more data are available from this study.

**Limitations**

The major limitation of this study is the low number of patients enrolled. The reasons for this low enrolment are detailed above. In addition, enrolment for this pre-specified substudy was not stratified, leading to an inequality of patient numbers within the PCI and CABG groups. However, despite the lack of randomization the baseline characteristics of both groups are similar, except for a longer duration of diabetes and more hyperlipidaemia in the PCI group compared with the CABG group.

Although most patients in the substudy had proven ischaemia, nine patients did not. These patients were entered into the CARDia study based on symptoms and angiographic stenoses considered significant by a multidisciplinary meeting. Guidance with invasive assessments of all coronary stenosis using FFR was not standard practice at the time of recruitment.

Stress echocardiography was used to assess ischaemia burden in this study. Stress echocardiography has been shown to have similar sensitivity and specificity to both MPS and stress perfusion cardiac MRI for the detection of significant CAD, when these modalities

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**Table 2** Results for coronary artery bypass grafting vs. percutaneous coronary intervention patients in myocardial function substudy

<table>
<thead>
<tr>
<th></th>
<th>CABG</th>
<th>PCI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible ischaemia improved (%)</td>
<td>87</td>
<td>79</td>
<td>0.9</td>
</tr>
<tr>
<td>No improvement in reversible ischaemia (%)</td>
<td>9</td>
<td>13</td>
<td>0.8</td>
</tr>
<tr>
<td>Worsening of ischaemia (%)</td>
<td>4</td>
<td>8</td>
<td>0.5</td>
</tr>
<tr>
<td>No ischaemia detected (n)</td>
<td>6</td>
<td>3</td>
<td>0.09</td>
</tr>
<tr>
<td>WMSI(pre)</td>
<td>1.69</td>
<td>1.63</td>
<td>0.9</td>
</tr>
<tr>
<td>WMSI(post)</td>
<td>1.46</td>
<td>1.32</td>
<td>0.8</td>
</tr>
<tr>
<td>WMSI(change)</td>
<td>0.23</td>
<td>0.31</td>
<td>0.8</td>
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are compared with invasive coronary angiography. It is possible that using an alternative non-invasive technique to assess for ischaemia or using more than one technique to assess for ischaemia may have led some or all of the nine patients without ischaemia at baseline being reclassified as having ischaemia. The CARDia study reflects contemporary management of coronary disease in diabetic patients; so it is also conceivable that a proportion of diabetic patients with multivessel coronary disease that undergo revascularization do not have a significant detectable ischaemic burden, either due to balanced ischaemia or due to an overestimation of the severity of coronary stenosis with angiography.

The follow-up for this study is for 6 months only. The purpose of this study was to compare reductions in ischaemic burden between PCI and CABG in diabetic patients. Reducing in ischaemic burden was considered as a surrogate of completeness of coronary revascularization. Further assessment at latter time points may show the attrition of the benefit of ischaemia reduction over time with either PCI or CABG. This may have led to an underestimation of the completeness of coronary revascularization with either technique.

**Conclusion**

The optimal form of revascularization in diabetic patients with multivessel disease remains controversial. This subset analysis of the CARDia trial in diabetic patients undergoing stress echo at baseline and at 6 months post-revascularization suggests that both PCI and CABG may achieve similar improvement in myocardial function and relief of ischaemia.

**Conflict of interest:** A.K. has received an unrestricted grant for research from Boston Scientific, received honoraria from Eli Lilly, and received educational grants from Cordis and Terumo. K.J.B. has received honorarium, travel grants, and speaker fees from Boston Scientific, Cordis, Biosensors, Abbott, and Medtronic.

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Interrupted aortic arch accompanied by a giant saccular aneurysm in a 53-year-old man

Wei Yu, Chun-Juan Chen, Xin Wang, Xin Zeng, and Wei Wang*
Department of Cardiology, The First Affiliated Hospital of Shantou University Medical College, No. 57, chang-ping Road, Shantou 515041, Peoples’ Republic of China
* Corresponding author. Tel: +86 754 88905462, Fax: +86 754 88258290, Email: janey_stu@yahoo.cn

A 53-year-old man with history of polyarteritis was admitted for chest distress and breathlessness. Physical examination showed the blood pressure was significantly greater in the right arm than in the left arm (right 180/90 mmHg vs. left 140/80 mmHg). Grade III systolic murmur was heard at the three to four left intercostal space. Transthoracic echocardiography revealed moderate tricuspid regurgitation, and pulmonary hypertension (estimated pulmonary pressure 36 mmHg). Subsequently, an ECG-gated contrast-enhanced multi-slice computed tomography (MSCT) angiography was performed to clarify the aortic morphologic conditions. MSCT axial and 3D reconstruction images clearly revealed a total absence of aortic arch, and a giant saccular aneurysm of descending thoracic aorta (Figure 1). Multiple twisted ramus anastomoticus rasing from right subclavian artery supplying the descending aorta. The patient was referred to thoracic surgery and a single AO-DA bypass graft was implanted.

Interrupted aortic arch (IAA) is a very rare congenital cardiovascular disease. In IAA, 95% of cases present with other congenital anomalies such as truncus arteriosus, aortic stenosis, transposition of great arteries, and ventricular septal defects. But no cases of IAA accompanied by a aneurysm has been reported in the medical literature. We first report such a case by MSCT angiography and 3D reconstruction.