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Coronary Revascularisation in Diabetic Patients with Multivessel Disease; Coronary Artery Bypass Grafting versus Percutaneous Coronary Intervention

Shabnam Rashid*

Leeds General Infirmary, Great George Street, Leeds, West Yorkshire, LS1 3EX, UK

***Corresponding author**: Dr Shabnam Rashid, BSc, MBChB, Leeds General Infirmary, Great George Street, Leeds, West Yorkshire, LS1 3EX, UK, Tel: 0113 2432799, Fax: 0113 3925751; E-mail: shabnamrashid@doctors.org.uk

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Abstract

Patients with diabetes mellitus and coronary disease have a higher mortality compared to individuals with coronary disease in the absence of diabetes mellitus. A significant proportion of patients with diabetes mellitus have combined risk factors for coronary artery disease including hypertension and hyperlipidaemia. The presence of underlying chronic inflammation and endothelial dysfunction further adds to the increased incidence of coronary disease in these patients. Revascularisation is indicated in patients with severe coronary artery disease. Coronary artery bypass grafting is recommended over percutaneous coronary intervention in patients with diabetes mellitus and multivessel disease as several trials have demonstrated the superiority of coronary artery bypass grafting in these patients. Major adverse cardiovascular and cerebrovascular events are higher in diabetic patients with multivessel disease who undergo percutaneous coronary intervention when compared to coronary artery bypass grafting.

Introduction

Approximately 25% of patients who undergo coronary revascularisation have diabetes mellitus (DM). Multiple trials have demonstrated the superiority of coronary artery bypass grafting (CABG) over percutaneous coronary intervention (PCI) in diabetic patients with multivessel disease [1-7]. The current European of Society Cardiology guidelines and the American Heart Association guidelines recommend CABG over PCI for patients with DM and multivessel disease as a class IIa indication [8,9]. Patients with DM and coronary disease have a twofold increase in mortality over 5 to 8 years after PCI compared to patients who undergo PCI without diabetes [10,11]. However, there is no mortality difference in diabetics and non-diabetics that undergo CABG. The presence of DM is an independent risk factor for restenosis after PCI and repeat revascularisation is often required in these patients. Approximately 80% of patients with diabetes die from a thrombotic cause, 75% due to an acute coronary syndrome and the remainder due to cerebrovascular events and complications secondary to peripheral vascular disease [12].

Discussion

The pathophysiology in patients with DM and coronary disease is complex and multifactorial. Up to 97% of patients with DM have dyslipidaemia with elevated triglycerides and low levels of high density lipoproteins. Hypertension further increases the risk for coronary disease.

Insulin resistance causes dyslipidaemia and endothelial dysfunction contributing to abnormalities in coronary blood flow. The presence of chronically low levels of inflammation in individuals with DM may precede or be the cause of insulin resistance [12]. Chronic inflammation is a known precursor for cardiovascular disease [13]. Furthermore, a reduction in nitric oxide, a vasodilator, and increased production of growth factor endothelin-1 promotes vasoconstriction as well as the release of pro-inflammatory cytokines. Proinflammatory cytokines cause injury by promoting reactive oxygen radicals and apoptosis of cells. Leukocyte accumulation in diabetic patients during ischaemia further increases the production of reactive oxygen radicals resulting in tissue damage. DM induces a hypercoaguable state with enhanced platelet activation and aggregation. A higher incidence of plaque rupture and thrombosis in diabetic patients occurs when compared to non-diabetic patients. This results in an acute coronary syndrome and often the diagnosis can be delayed in diabetic patients due to the atypical presentation. Patients maybe in acute heart failure, cardiogenic shock or sustain an arrhythmia. The delay in diagnosis may contribute to the morbidity and mortality seen in diabetic patients. These factors in combination may explain the poor outcomes that are prevalent in patients with diabetes after an acute coronary syndrome when compared to patients without diabetes [12].

CABG *vs.* balloon angioplasty

Despite advances in PCI, patients with DM continue to have higher major adverse cardiovascular and cerebrovascular events (MACCE) with PCI when compared to CABG. Prior to the era of drug and bare metal stents, balloon angioplasty was often the method for revascularisation. Several trials have assessed outcomes in diabetic patients with multivessel coronary disease who were revascularised with CABG or PCI. In the BARI study, a retrospective analysis of 353 patients with DM and multivessel disease, demonstrated that prognosis was better with CABG than balloon angioplasty. There was a 5 year survival advantage of having CABG over PCI with a mortality of 5.8% *vs.* 20.6% respectively (P=0.0003). The excess mortality rates in the PCI group was predominantly due to a cardiac cause. The patency of the internal mammary artery graft post CABG was felt to contribute to the reduction in mortality rates in both diabetic and non-diabetic patients. In this study patients were not randomised to the use of the internal mammary artery graft and therefore the survival advantage maybe due to factors related to patient suitability for the use of the

internal mammary artery graft. In diabetic patients who had CABG cardiac mortality post CABG was 2.9% when one internal mammary artery was used and 18.2% when saphenous vein grafts were used. This was similar to that of patients having PCI (20.6%). Patients without DM had similar cardiac mortality and myocardial infarction rates regardless of treatment with CABG or PCI [2]. The findings of the BARI trial were supported by the CABRI (Coronary Angioplasty *vs.* Bypass Revascularization Investigation) study, a large multicenter randomized trial comparing balloon angioplasty with CABG in patients with multivessel disease [5]. In contrast, the Emory Angioplasty *vs.* Surgery Trial (EAST) failed to show a survival advantage for CABG [14]. The limitations of both these trials was the low number of diabetic patients recruited therefore the results maybe underpowered to make firm conclusions. However, a meta-analysis of trials showed excess mortality with balloon angioplasty when compared to CABG in patients with diabetes. Mortality rates were similar amongst patients who underwent CABG regardless of the presence or absence of DM. Therefore in patients with DM and multivessel disease it is recommended to have CABG over PCI [15].

CABG *vs.* DES

Following the development of DES, the outcomes of patients with DM and multivessel disease being treated with drug eluting stents (DES) or CABG have been assessed. The CARDia (Coronary Artery Revascularization in Diabetes) was the first randomized trial of coronary revascularization with DES or CABG in diabetic patients with symptomatic multivessel coronary artery disease. The composite rate of death, myocardial infarction and stroke at 1 year was 10.5% in the CABG group and 13.0% in the PCI group (p=0.39), all-cause mortality rates was similar in both groups. PCI was therefore non inferior to CABG [16]. However, in the FREEDOM trial CABG was superior to PCI with sirolimus and paclitaxel DES in patients with DM and multivessel disease. Three vessel disease was present in 83% of patients. The composite primary outcome of death from any cause, non-fatal myocardial infarction and non-fatal stroke at 30 days was lower in the PCI group but not statistically significant. At 1 year follow up there was a significantly higher MACCE in the PCI group of 16.8% and 11.8% in the CABG group (P=0.004). This difference was driven by the requirement for repeat revascularization in the PCI group of 12.6% of patients *vs.* 4.8% of patients in the CABG group (P<0.001). A further 5 year follow up demonstrated a significantly lower MACCE rates in the CABG group when compared to PCI; 18.7% and 26.6% respectively, a relative risk reduction of 30%. All causes of mortality was higher in the PCI group at 16.3% and 10.9% in the CABG group. Myocardial infarction was also higher in the PCI group; 13.9% *vs.* 6% in CABG group. However, strokes occurred less frequently in the PCI group than in the CABG group; 2.4% *vs.* 5.2% respectively (P=0.03). Stroke was highest among patients undergoing CABG in the early post procedural period. Therefore, CABG was superior to PCI with DES in patients with DM and multivessel coronary disease as there was a significant reduction in the rates of death and myocardial infarction in the CABG group but with higher stroke rates [1]. The SYNTAX study also showed higher MACCE at 12 months when DES were used in patients with DM and left main stem disease (LMS) when compared to CABG. In the SYNTAX study PCI with paclitaxel eluting stent was compared with CABG in all patients with LMS disease. DM was present in 25% of the patients in the PCI and CABG group. The MACCE rates at 1 year were similar for patients who had CABG or PCI (13.7% *vs.*15.8% respectively *P*=0.44). Stroke events were significantly higher in patients who had a CABG; 2.7% *vs.* 0.3% PCI; *P*=0.009. However, the requirement for repeat revascularization was significantly higher in the PCI group of 6.5% and 11.8% in the CABG group *P*=0.02. The combined safety end point of all death, cerebrovascular and myocardial infarction rates were similar between both groups at 1 year (9.1% CABG *vs.* 7.0% PCI) [4]. At 5 year follow-up the MACCE rates were 36.9% in PCI patients and 31.0% in CABG patients P=0.12. Stroke rates remained significantly higher in the CABG group; 4.3% *vs.* 1.5% in the PCI group p=0.03. Repeat revascularization also remained higher in the PCI arm (26.7% *vs.* 15.5% P<0.01). When the MACCE rates were analysed based on the SYNTAX score then the event rates were similar in both groups of patients with low/intermediate SYNTAX scores but increased significantly in PCI patients with high scores ≥ 33 [17]. The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score is an independent predictor of 1 year mortality rate, cardiac death, myocardial infarction and target vessel revascularisation. The syntax score is used for risk stratification in patients with multivessel disease and LMS disease. The SYNTAX score is calculated based on patient characteristics and angiographic appearance of the coronary arteries. Patients with a higher SYNTAX score are likely to have greater risk posed if undergoing PCI [18]. The subgroup of LMS patients with DM consisted of 67 patients. The observed MACCE rates were similar between DM and non DM with the only statistical difference being an increased need for repeat revascularisation with PCI in diabetic patients [18]. Based on the subgroup analysis of diabetic patients the trial was underpowered for analysis. In diabetic patients with LMS disease PCI may not be suitable due to the increased need for repeat revascularisation. However, CABG and PCI are potential feasible options for treatment of LMS disease in non-diabetic patients. Before deciding on the treatment strategy the extent of coronary disease should be analysed as patients with a high SYNTAX scores appeared to benefit from surgery when compared to those with lower SYNTAX scores.

In the Arterial Revascularization Therapies Study (ARTS) a subgroup analysis of 208 patients with DM and multivessel disease who had CABG or PCI showed that mortality was higher in the PCI group 13.4% *vs.* 8.3% in the CABG group (p=0.27) at 5 year follow-up. Mortality was highest amongst diabetic patients who underwent PCI when compared against non-diabetics who had PCI (13.4% *vs.* 6.8% p=0.03). The 5 year MACCE rate in diabetic patients treated with PCI was 54.5%, *vs.* 38.7% in non-diabetics (p=0.003) and was largely driven by the need for repeat revascularization in diabetic patients (42.9% *vs.* 27.5%, p=0.002). Diabetic patients who had PCI had a cardiac cause for death in 50% of cases *vs.* 38% in non-diabetic patients who underwent PCI (p=0.43). There was no significant mortality difference or MACCE rates between diabetic and non-diabetic patients within the CABG group [3]. This would suggest that CABG is the optimal treatment strategy in patients with DM and MVD.

Small subgroup analysis of diabetic patients with multivessel disease randomised to PCI or CABG have demonstrated higher mortality in diabetic patients undergoing PCI when compared to non-diabetics (10% *vs.* 6.4% respectively p=0.663). The 5 year mortality amongst diabetic patients undergoing CABG was not statistically different to non-diabetics 10.2% and 11.8% respectively (p=0.637). The limitations from this study was the low number of diabetics analysed since the results were extrapolated from 39 diabetic patients [6].

In a prospective, multicenter study, 198 patients with diabetes with severe coronary artery disease were randomly assigned to CABG or PCI. After a mean follow-up period of 2 years, all-cause mortality was

5.0% for CABG and 21% for PCI, nonfatal myocardial infarction occurred in 15% of patients and 6.2% respectively. The study was terminated due to slow recruitment since only 25% of the intended sample size was recruited therefore underpowered for the primary composite endpoint of death and nonfatal myocardial infarction. Furthermore the confidence intervals were very large [7].

Conclusion

Major adverse cardiovascular and cerebrovascular events are higher in diabetic patients with multivessel disease who undergo PCI when compared to CABG. The event rates appear to be driven by the requirement for repeat revascularisation in patients who undergo PCI. However, despite the positive outcomes with CABG, stroke rates are higher in the early post procedural period.

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