ABSTRACT

Diabetes is challenging for revascularization due to specific disease related high risk clinical and angiographic features. In the early 90's CABG was the preferred modality of revascularization in diabetics with multivessel disease due to high rate restenosis rates with percutaneous angioplasty alone (POBA) and bare metal stents (BMS). With advent of drug eluting stents (DES) the role of PCI in mutivessel disease in diabetics is gaining more acceptance. However, the issues of late stent thrombosis and need for lifelong anti-platelet therapy need to be addressed. Due to social factors especially in our country and evidence based data, we feel, diabetic patients with TVD should surely be offered CABG. Patients with two vessel disease and diabetes need to be treated depending on type of lesions (A, B or C). Most diabetic patients with single vessel disease where PCI is feasible and lesions can be covered with single stent, PCI with DES can be offered. The result of ongoing randomized control trial (FREEDOM) may clarify the role of PCI with drug eluting stent and GP IIb/IIIa inhibitor versus CABG in diabetics who require multi vessel revascularization.

CAD IN DIABETICS

Diabetes mellitus is considered as a risk equivalent for coronary heart disease. Several clinical, angiographic and biological features are associated with coronary artery disease in diabetic population. (Table 1)

Diabetics have a lipid rich atherosclerotic plaque that is more vulnerable to rupture than non diabetics. These plaques exhibit enhanced vascular inflammatory reaction due to over expression of receptor for advanced glycation end products (RAGE), which enhances matrix metalloproteinase activity that can destabilize plaques. Additionally, platelets in diabetics exhibit enhanced aggregation and increased expression of activation dependent adhesion molecules, such as GP IIb/IIIa and CD 40 ligand, factors which contribute to thrombus formation. Also, diabetics have increased levels of plasminogen activator inhibitor type 1 (PAI-1) which decreases fibrinolysis, increases thrombus formation and accelerates plaque formation. In addition to these thrombogenic factors, changes in vascular function contribute to the poorer outcomes in diabetes. Vascular changes include increased endothelin activity and reduced prostacyclin and nitric oxide activity. No reflow following successful percutaneous recanalization of an infarct related coronary artery occurs more commonly in diabetics and may contribute to left ventricular dysfunction. No reflow probably results from platelet endothelial cell interactions that impair microvascular function and decrease myocardial blood flow.

Angiographic features related particularly to diffuse and distal coronary disease may lead to incomplete revascularization or increase the risk of surgical or percutaneous intervention in these patients. Diabetics usually have extensive multi vessel disease with angiographically small reference vessels, frequent left main
patients who underwent CABG (75.5%) compared with those who underwent PTCA (60.1%; \( p=0.23 \)). In the non diabetic population survival was 79.3% and 82.7% in the angioplasty and surgical group respectively. By 8 years, a repeat revascularization occurred more frequently in PTCA vs CABG treated patients (65.3% vs 26.5%) respectively (\( p<0.001 \)).

The BARI (Bypass Angioplasty Revascularization Investigation) study was designed to compare long-term survival in patients with multivessel disease and severe angina or ischemia randomized to PTCA or CABG.

The survival advantage (at 7 years) in the CABG group was largely confined to patients who had received an internal mammary artery (IMA) graft to the left anterior descending artery (LAD) (83.2%, \( n=140 \)) compared with those who had received only saphenous vein grafts (SVGs) (54.5%, \( n= 33 \)). The difference between the 2 groups was explained by the 353 patients with treated DM for whom estimates of 7-year survival were 76.4% and 55.7% in those treated by CABG and PTCA, respectively (\( p=0.001 \)). At 5 years, the BARI study showed 15 excess deaths for every 100 diabetic patients revascularized by PTCA compared with CABG, and at 7 years this difference increased to >20. In the BARI study, CABG was associated with better survival in the randomized diabetic patients (\( n=353 \); however, in the registry patients (\( n=339 \)), there was no difference.

The 10-year survival was 71.0% for PTCA and 73.5% for CABG (\( p=0.18 \)). At 10 years, the PTCA group had substantially higher subsequent revascularization rates than the CABG group (76.8% vs. 20.3%, \( p=0.001 \)), but angina rates for the 2 groups were similar (Figure 1 & 2). There was no significant long-term disadvantage regarding mortality or myocardial infarction associated with an initial strategy of PTCA compared with CABG. Among patients with treated diabetes, CABG conferred long term survival benefit, whereas the 2 initial strategies were equivalent regarding survival for patients without diabetes. The greater protective effect

**TREATMENT OPTIONS**

The modalities for myocardial revascularization in diabetics are:

1. **CABG**
2. **PTCA (POBA)**
3. **PCI with bare metal stents**
4. **PCI with drug eluting stents**

Conventionally, patients with single and double vessel disease with type A or B lesions are considered suitable for PCI while patients with triple vessel disease, Left Main Coronary Artery (LMCA) disease and type C multi vessel disease are considered suitable for CABG. Patients with diabetes have smaller vessels, more thrombotic complications higher incidence of LV dysfunction and increased restenosis rates. Therefore, the choice of therapy between these 2 options (CABG vs PCI) is somewhat different in diabetics than in non diabetics. Also most trials have shown that diabetics fare less well with PCI as compared to CABG than the non diabetic population. We now review the progress in the last three decades between these approaches of myocardial revascularization.

**CABG VERSUS PTCA (POBA)**

TRIALS – The EAST study, The BARI study, CABRI study (1987-2002)

The Emory angioplasty versus Surgery Trial (EAST) was a single center randomized comparison of a strategy of initial coronary angioplasty (\( n=198; 49[24.7\%] \) DM) or coronary bypass surgery (\( n=194; 41[21.2\%] \) DM) for patients with multi vessel coronary artery disease. Survival at 8 years tended to be greater in diabetic patients who underwent CABG (75.5%) compared with those who underwent PTCA (60.1%; \( p=0.23 \)). In the non diabetic population survival was 79.3% and 82.7% in the angioplasty and surgical group respectively. By 8 years, a repeat revascularization occurred more frequently in PTCA vs CABG treated patients (65.3% vs 26.5%) respectively (\( p<0.001 \)).

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of CABG can probably be explained by the more extensive revascularization.

In the CABRI study a (Coronary angioplasty versus bypass revascularization investigation study) 4-year mortality and level of pre- and post-revascularization angiographic CAD were compared between both diabetics and nondiabetics and between revascularization modes in the PTCA versus CABG population as a whole, and then stratified by diabetic status and then by procedure to which they were randomized (n=1,054) (125 diabetics (11.9%)). Diabetics had significantly greater mortality than non-diabetics (RR 2.19, P = 0.001) which was more likely related to more rapid disease progression than to greater post-revascularization disease. Among diabetics or nondiabetics, there was no significant mortality difference between those randomized to PTCA versus those to CABG.

A meta-analysis of 13 randomized controlled trials(n=7,964) comparing CABG with PTCA suggests that CABG is associated with a lower five-year mortality, less angina, and fewer revascularization procedures. For patients with multivessel disease, CABG provided a survival advantage at five to eight years, and for diabetics, a survival advantage at four years.

**CABG versus PCI with BMS (1995-2005)**

With the progress in PCI techniques and use of bare metal stents improvement in immediate outcomes was realized by controlling two recognizable factors responsible for restenosis – elastic recoil and negative re-modelling. Restenosis after stenting caused by neointimal hyperplasia is increased in diabetic population. In a meta analysis of six studies, including 1166 diabetic patients with stent PCI, the average restenosis rates among patients with diabetes was 36.7%.5 The ARTS (Arterial Revascularization Therapy Study) trial compared outcomes from bypass surgery versus coronary stenting in patients with multivessel disease. In diabetic patients treated with stenting, the event-free survival at 1 year was 63.4% as compared with diabetic patients treated with CABG (84.4%) (p < 0.001). In the non diabetic patients treated with stenting and CABG event-free survival at 1-year was 76.2% & 88.4% respectively. This difference was largely due to higher incidence of repeat revascularization and a lower rate of complete revascularization in patients who underwent PCI (70.5%), as compared with those who had CABG (84.1%; p < 0.001). The 5-year mortality rate of diabetic patients in the stent group was 13.4% compared with 8.3% in the surgical group (RR 1.61, 95% CI 0.71 to 3.63). Within the stent group, the mortality of diabetic patients remained higher than that of nondiabetic patients (13.4% vs. 6.8%; p = 0.03), whereas it was similar in the surgical group (8.3% vs. 7.5%; p =0.8).6

In the ERACI IIa study (n=450, 17.3% diabetics) PTCA with BMS implantation was compared with CABG in symptomatic patients with multi vessel CAD. 30 day, 1, 3 and 5 year follow up was done. During the first 30 days, PTCA patients had lower major adverse events (3.6% vs. 12.3%, p =0.002), death (0.9% vs. 5.7% p < 0.013) and Q myocardial infarction compared with CABG patients. Similar 30 days (PCI vs. CABG) outcomes were observed in the diabetic subgroup.

At one year follow up, survival & freedom from MI was better in PTCA compared to CABG patients. Requirements for new revascularization procedures were higher in PTCA than in CABG patients (16.8% vs. 4.8%, p< 0.002). Hence, immediate and one-year follow-up results of the ERACI II study showed a prognosis advantage of PCI with stents over CABG.

At five years of follow-up, the survival rates were similar in PCI and CABG group (92.8% vs. 88.4%, p =0.16). Freedom from repeat revascularization procedures and freedom from major adverse cardiac events (MACE) was significantly lower with PCI compared with CABG. Similarly, in diabetic subgroup 5 year mortality rates in PCI and CABG groups were 10% and 10.2% respectively. Hence, there were no survival benefits from any revascularization procedure; however patients initially treated with CABG had better freedom from repeat revascularization procedures and from MACE.

The SOS (Stent Or Surgery) trial showed less repeat revascularization with CABG than with PCI overall at 2 years, but the diabetic subgroup was not analyzed separately. However, at median follow up of 6 years, a continuing survival advantage (10.9% mortality in PTCA vs. 6.8% in CABG group) was observed for patients managed with CABG, which is not consistent with results from other stent vs. CABG studies.

The Veterans Affairs AWESOME 10 (Angina With Extremely Serious Operative Mortality Evaluation) study of high-risk patients compared survival after PCI with survival after CABG among diabetics. The respective CABG and PCI 36-month survival rates for diabetic patients were 72% and 81% for randomized patients, 85% and 89% for patient-choice registry patients, and 73% and 71% for the physician-directed registry patients. None of the differences was statistically significant. It was concluded that PCI is a relatively safe alternative to CABG for diabetic patients with medically refractory unstable angina who are at high risk for CABG.

In spite of the significant impact of stents in the reduction of restenosis and the need for subsequent revascularizations within the first year, diabetic patients continued to have high in-stent restenosis rates and diabetes continued to be an independent risk factor for adverse outcomes. Therefore, in the bare metal stent era, surgery remained the preferred therapy for diabetic patients with multi vessel CAD.

**CABG versus PCI with DES (2002 – onwards)**

DES elute anti proliferative agents to reduce neointimal hyperplasia. Hence, their introduction was considered to be ideal for diabetic patients where the restenosis limitation of PCI is more significant. However, increased rates of stent thrombosis has been a matter of concern particularly in diabetic patients. Using registry data from Rotterdam 11 the incidence was similar...
among BMS (1.4%), sirolimus eluting stents (1.5%) and paclitaxel eluting stents (1.6%). Diabetes was the only predictor of stent thrombosis. In another multi centre registry, the nine month cumulative stent thrombosis rate was 1.3% (0.8% with sirolimus and 1.7% with paclitaxel). Diabetes was an independent predictor of sub acute stent thrombosis (from procedure to 30 days), but not of late thrombosis, the main predictor being premature antiplatelet treatment discontinuation. However, the data of late stent thrombosis in diabetics is still limited hence, empirical clinical recommendations are for a longer use of dual antiplatelet treatment in diabetics, eventually for life.

In the SIRIUS\cite{12} & TAXUS IV trial there was a subgroup of 131 & 155 diabetic patients with sirolimus eluting and paclitaxel slow release stents. Reference vessel diameters (2.75 mm and 2.72 mm) and lesion lengths (14.5 mm and 14.2 mm) were similar in the diabetics of these two trials. The clinical benefits of DES versus BMS at 12 months showed significant risk reduction i.e., low rates ofTLR (6.9% and 7.4%), TVR (9.9% and 11.3%), target vessel failure (TVF) (12.2% and 15%) and MACE (9.2% and 15.6%). Mortality and rates of MI were similar. Because diabetic patients did not represent a pre-specified subgroup in these studies, the role of DES for diabetic patients has been questioned. A thick strut BMS, used in the control group of these trials probably enhanced the apparent anti-restenotic effects of the new DES. The DIABETES (Diabetes and Sirolimus-Eluting Stent) trial specifically assessed the effects of a sirolimus-eluting stent (SES) in DM\cite{13}. Notably, late loss at stent edges was similar in the SES and BMS groups. This might be explained by relative drug sparing at the edge of the stent, injury at the peri stent zone, and geographic miss. The SIRTAX (Sirolimus- versus paclitaxel-eluting stents) trial\cite{14} suggests that Sirolimus eluting stent (SES) might be preferred to paclitaxel-eluting stent (PES) for PCI in DM.

In the SYNTAX (Synergy between percutaneous coronary intervention with Taxus and cardiac surgery) study\cite{15}(n=1800,897 to CABG and 903 to DES – PCI; 28.3% diabetics) the reduction in MACE with CABG was driven by a lower rate of repeat revascularizations compared with PCI (5.9% vs 13.7%, p = 0.0001). Neither death nor MI rates differed between the two groups, but there was a higher rate of CVA with CABG (2.2% versus 0.6%, p=0.003). Subgroup analysis revealed that the CABG benefit was greatest in patients with diabetes, for whom the 1 year MACE rate was 14.2% with CABG versus 26.0% with PCI (p=0.0025). Corresponding rates in non diabetic patients were 11.8% versus 15.1% (p=0.08).

The CARDIA trial is the largest prospective investigation specifically into the optimal strategy for revascularization of diabetic CAD, with 510 patients randomized into either PCI with abciximab and stents or CABG treatment arms. No significant difference was seen between the two treatment arms for the composite clinical endpoint (11.6% for PCI, 10.2% for CABG, p=0.63), or for the individual variables of death (3.2% for PCI, 3.3% for CABG, p=0.83) and CVA (0.4% for PCI, 2.5% for CABG, p=0.09). The rate of repeat revascularization was higher for patients receiving PCI (9.9%) versus those in the CABG arm (2.0%). In a sub study from CARDIA trial\cite{16}, in terms of repeat revascularization, there is an advantage with DES versus BMS (7.3% versus 17.3%, p=0.023) in patients with diabetes and multivessel disease.
In the Washington Hospital Center, 1680 patients with multivessel CAD undergoing revascularization with either CABG or PCI with DES over an 18-month period (from 10/2003 to 12/2004) were evaluated (1080 patients with two vessel disease and 600 with triple vessel disease). The MACE was reduced with CABG (particularly in diabetics) for patients with two vessel disease (9.7% CABG versus 21.2% PCI; P<0.001) and triple vessel disease (10.8% CABG versus 28.4% PCI; P<0.001). Hence, it was concluded that coronary artery bypass surgery may be the preferred revascularization strategy in diabetic patients with multivessel coronary artery disease. (Figure 3 & 4) Similar results were obtained in another study which included 9963 patients receiving drug-eluting stents and 7437 patients undergoing CABG followed up for period of one year. Hazard ratio for death was 0.80 in patients with TVD and 0.71 in patients with DVD undergoing CABG when compared to those who received a drug eluting stent. It was found that for patients with multivessel disease, CABG continued to be associated with lower mortality rates than did treatment with drug-eluting stents. CABG was also associated with lower rates of death or myocardial infarction and repeat revascularization in these patients.

Novack et al report the 1 year outcomes from the EVENT registry which included 9963 patients receiving drug-eluting stents and 7437 patients undergoing CABG followed up for period of one year. Hazard ratio for death was 0.80 in patients with TVD and 0.71 in patients with DVD undergoing CABG when compared to those who received a drug eluting stent. It was found that for patients with multivessel disease, CABG continued to be associated with lower mortality rates than did treatment with drug-eluting stents. CABG was also associated with lower rates of death or myocardial infarction and repeat revascularization in these patients.

CONCLUSIONS
Diabetes is challenging for revascularization due to specific disease related high risk clinical and angiographic features. Poor outcomes after CABG have been described due to increased incidence of wound infection, cognitive decline, stroke, poor quality of life and high 12 month incidence of death or SVG stenosis. Similarly adverse outcomes after PCI have been identified in diabetics. They have higher procedural complications, in hospital mortality, increased length of stay, renal dysfunction, increased rates of stent thrombosis, instant restenosis and native disease progression. In the early 90’s studies which compared POBA with CABG showed distinct and definite advantage of CABG over POBA due to its high restenosis rates in diabetic population. The trials in late 90’s with BMS PCI compared to CABG showed decrease of this gap in the non diabetic population. However, amongst diabetics the need for revascularization was more due to significant restenosis. With the advent of DES we initially felt the results would be comparable in two sub groups. This had proven to be true in non diabetic population. However, amongst diabetics CABG continues to hold an edge over multi vessel PCI. Recently, a report from the EVENT registry (June 2009) found similar one year outcomes with multivessel DES in patients with and without diabetes. Also, particularly in our country the factor of need for revascularization, which may not be as significant in state paid or insurance paid health care nations, is a much more bigger factor in choosing the initial form of therapy. Due to this social factor and evidence based data we feel diabetic patients with TVD should surely be offered CABG. Patients with two vessel disease and diabetes need to be treated depending on type of lesions (A, B or C). Most diabetic patients with single vessel disease where PCI is feasible and lesions can be covered with single stent, PCI with DES can be offered. Newer issues like high incidence of stent thrombosis and need for life long antiplatelet therapy should be kept in mind before offering one amongst two forms of therapy. More rapid, consistent, and potent platelet antagonists, platelet function assays, as well as more complete endothelialization of later generation DES hold the unproven promise of mitigating the stent thrombosis risk in diabetics.

Several evolving management strategies for multivessel disease in diabetics include more aggressive medical therapies, hybrid PCI-CABG procedures, minimally invasive CABG, fractional flow reserve/functional test guided revascularization, and appropriately staged revascularization approaches. Particularly in higher-risk diabetic patients with impaired renal function, incremental...
revascularization with provisional staged procedures driven by clinical response and serial functional testing may provide superior outcomes to a set piece strategy based on the index angiographic anatomy.

Surely, in the era of DES and dual antiplatelet therapy, the role of PCI in diabetics is gaining more acceptance. However, the issues of late stent thrombosis still need to be addressed. The result of ongoing randomized control trial (FREEDOM) may clarify the role of PCI with drug eluting stent and GP IIb/IIIa inhibitor versus CABG in diabetics who require multivessel revascularization.

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