



Coronary Artery Bypass Graft Surgery (CABGS) Continues to be Treatment of Choice in Multivessel Coronary Artery Disease: I Beg to Differ?

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The treatment of multivessel coronary artery disease (CAD) continues to be a matter of exciting debate. The rapid developments in percutaneous coronary intervention (PCI) technology and pharmacotherapy are already changing the direction of our therapeutic strategies. It is quite amazing to hear debates like “whether coronary artery bypass surgery (CABGS) will be a technique of past” and also to read in the press about closure of certain surgical suites in USA. It is also a fact that large number of percutaneous interventions are being done as compared to CABGS in USA and Europe and there has been tremendous growth of interventional cardiac catheterization laboratories all over the world. A debate has been initiated entitled “Coronary Artery Bypass Graft Surgery (CABGS) continues to be treatment of choice in multivessel Coronary Artery Disease (CAD)?” The purpose of this article is to convey the views of clinical and interventional cardiologists which beg to differ.

The optimal management of stable angina pectoris with multivessel CAD remains multi-dimensional, but therapeutic options include medical therapy, PCI or CABGS. The three potential reasons to recommend revascularization are 1) to alleviate symptoms of myocardial ischemia, 2) to reduce the risk of future mortality, and 3) to treat and prevent morbidities such as myocardial infarction (MI), arrhythmias or heart failure (HF).

For this article, the following issues will be discussed.

- 1) Current status of medical therapy vs CABGS.
- 2) Growth of PCI technology.
- 3) Current status of PCI vs CABGS.
- 4) Status of off pump surgery.

CURRENT STATUS OF MEDICAL THERAPY VS. CABGS

The earlier trials comparing CABGS with medical therapy indicate that the mortality benefits of CABGS are proportional to baseline patient risk. CABGS is effective for symptom improvement, however, does not reduce the overall incidence of nonfatal MI. The maximum advantage of CABGS has been reported for high risk patients such as those with left main, severe three vessel disease and in those with left ventricular (LV) dysfunction.¹

The trials comparing percutaneous transluminal balloon angioplasty (PTCA) to medical therapy suggest that PTCA provides better symptomatic benefit, however, does not prevent

death or MI. Balloon angioplasty is associated with a greater need for subsequent CABGS. The addition of stents (bare metal) decrease rate of angiographic restenosis and repeat procedures but not those of death or MI.¹ The data from drug eluting stents vs. medical treatment is currently not available.

The medical treatment in recent years has undergone a sea change and includes new beta-blockers, low molecular weight heparin, newer anti-platelet agents (Clopidogrel), statins, ACE inhibitors and AT – 2 blockers.

The recent publication of MASS II trial,² has given a fresh fillip to the debate of optimal management (medical vs PCI vs CABGS).³ There was no statistically significant difference between CABG, PCI and medical treatment groups with regard to cardiac mortality or acute MI at one year follow up (1 year survival rates 96.0% for CABG, 95.6% for PCI and 98.5% for medical treatment; one year survival free of Q wave MI, 98% for CABG, 92% for PCI and 97% for medical treatment). The CABGS and PCI-treated patients had better relief of angina (88% angina-free at one year as compared to 79% for PCI and 46% for medically treated group, $P < 0.0001$). In this trial, patients with Class II or III stable angina and preserved LV function were included. These results suggest that modern medical treatment in selected patients can result in 1 year survival which is comparable to CABGS or PCI. However, medical treatment does not relieve angina as effectively as does CABGS or PCI.

In MASK II trial, drug eluting stents (DES) and GP IIb/IIIa inhibiting agents were not utilized in the PCI arm. Similarly in the surgical arm, off pump surgery was not utilized. The results of PCI or CABGS would have been different if these techniques were utilized.

GROWTH OF PCI TECHNOLOGY

Twenty five years after its tentative beginnings, PCI has become the dominant form of coronary revascularization. The substantial growth of plain old balloon angioplasty (POBA) through out 1980s and early 1990 was largely because of refinement of guidewires and low profile balloons. However, the greatest technological advance since 1994 has been in the development of stents. In addition, there have been effective adjuvant antiplatelet regimens (ticlopidine, clopidogrel and glycoprotein IIb/IIIa inhibitors). A plethora of randomized trials demonstrate that glycoprotein IIb/IIIa agents are very effective in reducing periprocedural MI.

The results of the trials using balloon angioplasty and stents differed in two important ways.⁴ In the balloon angioplasty trials, the frequency with which urgent or emergency CABGS was required in the PCI arm during the index hospitalization ranged from 5% to 10%, whereas in the stent trials, fewer than 1% of PCI patients required urgent or emergency CABG. The second difference relates to the frequency of restenosis in the PCI arms of the trials. Those trials in which stents were used had less than half the frequency of restenosis and target vessel revascularization of the earlier balloon angioplasty trials. It became quite obvious from the results of randomized trials that better acute results, reduced emergency surgery and reduced restenosis are attainable by bare metal stents and adjunctive pharmacotherapy.

The restenosis continues to be a challenge in PCI and devices like rotablation, directional atherectomy and laser angioplasty could not reduce the incidence. Intracoronary radiation in selected cases reduces restenosis. However, the most exciting advance for reducing restenosis is advent of drug eluting stents (DES). The DES acts as a drug delivery device to reduce restenosis. The first of these was the sirolimus-coated cypher stent. Sirolimus is one of several agents that have powerful antimitotic effects and inhibit new tissue growth inside the artery and stent. Paclitaxel, everolimus and several other cytotoxic agents have become available for stent coatings. By reducing the incidence of restenosis (and therefore recurrent symptoms), DES are tilting the balance of treating CAD in favour of percutaneous intervention rather than CABGS.

CURRENT STATUS OF PCI VS CABGS

Percutaneous coronary intervention has become almost universally embraced as the preferred revascularization strategy for CAD patients in the US, where now more than 1 million such procedures are performed annually. There are nearly 11 randomized trials comparing an initial strategy of PCI versus CABGS in the treatment of patients with multivessel CAD. Six of these trials used balloon angioplasty in the PCI arm, whereas the five most recent trials (of which ARTS was the largest with 1205 patients) used stents in the PCI arm. The results of these 11 trials were concordant in that both CABGS and PCI provide symptomatic benefits without altering the incidence of death or nonfatal MI. The frequency of death and MI in both arms was similar. Few trials included stroke as an end-point and exclusion of this end-point tilted the results in favour of CABGS. The repeat revascularization procedures in PCI patients are understandable and have reduced significantly in the bare metal stent era.^{1,4}

The Arterial Revascularisation Therapies Study Group (ARTS) trial⁵ enrolled 1205 patients with multivessel coronary disease in whom a cardiac surgeon and interventional cardiologist agreed that they could achieve a similar extent of revascularization. In this randomized comparison, there was no difference at 1 year in the combined rate of death, myocardial infarction (MI), and stroke between the two revascularization strategies. However, repeat revascularization rates were higher with stenting (16.8% versus 3.5% with surgery), with a net cost savings of \$2973 per patient favouring the stent approach. In patients with diabetes (n=198), the difference in repeat revascularization rates was even more disparate (22.3% with stents versus 3.1% with CABG), although overall event-free survival was similar.

Similar results were reported by the Stent or Surgery (SoS) trial investigators⁶ The trial randomized 988 patients with multivessel disease (57% two-vessel : 42 % three-vessel) to revascularization with PCI (78% received stents) or CABG (81% with pedicled left internal mammary artery (IMA) graft). The primary end-point of repeat revascularization occurred in 21% of PCI patients versus 6% of CABG patients at a median follow up of 2 years (hazard ratio equals 3.85, *P* less than 0.0001). Freedom from angina was also better with surgery (79% versus 66%). Mortality was higher in the PCI group but was influenced by a particularly low surgical mortality and a high rate of noncardiovascular death in the PCI group.

In the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) study,⁶ 454 patients at 16 VA hospitals with high risk features for adverse outcome with surgery were randomized to either surgery or PCI. High risk characteristics included prior open heart surgery, age greater than 70 years, ejection fraction less than 0.35, MI within 7 days, and the need for an intra-aortic balloon pump (IABP). Stents were used in 54% of PCI patients. Survival was similar (79% with CABG and 80% with PCI) at 36 months. Finally, in the Stenting versus Internal Mammary Artery (SIMA) trial, patients with isolated proximal left anterior descending CAD were randomly treated with stenting or CABG (using the IMA). At 2.4 years of follow-up, there were no differences in the rates of death, MI, functional class, medications, or quality of life. Repeat revascularization was required more often (31% versus 7%) in the stent group. Overall, six trials have now been published comparing CABG with PCI utilizing stents in single or multivessel disease. Compared with the earlier trials utilizing balloon angioplasty, stent usage and left IMA revascularization rates have increased. The results in terms of death, MI, and stroke are similar in the more recent trials; however, the disparity in the need for repeat revascularization, which favors surgery, has narrowed. It can also be argued that what relevance, if any, the results of trials comparing non-DES in CABGS have in the DES era.

From the above discussion, it is clear that if repeat revascularization can be reduced in the PCI group, the choice of revascularization will tilt against the CABGS. As we are all aware, PCI is comparatively less invasive, avoids thoracotomy, blood transfusion, leg incisions and promotes early discharge from the hospital. The drug eluting stents in the recent trials have shown promising results with marked reduction in restenosis rates as compared to bare metal stents. In a randomized controlled trial (RAVEL)⁷ cypher stent gave a six month restenosis rate of 0% compared with 27% for an uncoated stent of the same design. A later randomized study (SIRIUS)⁸ of more complex stenoses (which are more prone to recur) still produced a low rate of restenosis within stented segments (9% vs 36% with uncoated stents), even in patients with diabetes (18% vs 51% respectively). Other randomized studies⁹ such as ASPECT and TAXUS II have also shown that coated stents (with the cytotoxic agent paclitaxel) have significantly lower six month restenosis rates than identical uncoated stents (14% vs 39% and 6% vs 20% respectively). From the results of the DES trials,⁹ it seems likely that DES will result in similar reductions in the setting of multivessel PCI and thus in the abolition of the difference in repeat revascularization between CABGS and stenting. Given the approximate 7 %

frequency of in-hospital vein graft occlusion, DES may in fact be a more durable means of coronary revascularization than CABG using vein grafts.

The ongoing Arts – 2 trial using multiple DES vs CABGS should provide further data.

Diabetic patients with Multivessel disease

The appropriate revascularization strategy in diabetic patients with multivessel disease has been a subject of never ending debate.^{10, 11}

To address this uncertainty, several recent studies^{5, 6} have compared contemporary PCI (with the use of stents) and CABG among diabetic patients with multivessel CAD. Of these studies, three (ARTS, SoS, and ERACI-II) enrolled patients similar to those in the BARI trial, while the AWESOME (Angina with Extremely Serious Operative Mortality Evaluation) study enrolled a high risk population, based on clinical characteristics, that would not have been included in the BARI trial. Clinical follow-up in these studies is limited, with 1-3 year follow up currently reported. Mortality data for the entire cohort have been somewhat inconsistent, with the ERACHI trial reporting an early mortality benefit for PCI, the SoS (stent or surgery) trial reporting a mortality benefit for CABG at 2 years, and the ARTS (Arterial Revascularisation Therapy Study) and AWESOME trials demonstrating no mortality difference at 1 and 3 years, respectively. No mortality benefit was seen with CABG in the diabetic subset from AWESOME and ARTS.

Beyond mortality, CABGS remains superior to PCI-stenting in reducing the need for repeat revascularization during short to intermediate – term follow up (1-3 years). Specifically, in the diabetic subset of the ARTS trial, the 1-year repeat revascularization rate for CABG and PCI stent was 3.1 % and 22.3%, respectively ($p < 0.001$). This represents an approximate halving of the rates of revascularization with PCI stenting compared to historical studies using balloon angioplasty. Likewise, the most recent generation of bare metal stents has been associated with only a 10% rate of target vessel revascularization at 1 year for diabetics in contemporary PCI trials (TARGET, ESPRIT). The incidence of MI is not statistically different between surgical and percutaneous revascularization cohorts during intermediate term follow-up. Longer clinical follow-up of the PCI stent vs. CABG trials is required before firm conclusions can be drawn. Whatever the outcome, their interpretation will be hampered by the continued evolution of revascularization strategies.

In this regard, while the use of adjunctive glycoprotein (GP) IIb/IIIa inhibitors did increase significantly over the course of enrollment in most of the PCI-stent vs. CABG trials, the overall frequency of use was low, varying from 0% (ARTS) to 28% (ERACI-II). This may importantly influence the comparison of long-term mortality outcomes in these trials given the proven mortality benefit of adjunctive GP IIb/IIIa in diabetics undergoing PCI. Moreover, the recent introduction of sirolimus and paclitaxel eluting stents, with the potential of further reducing restenosis rates, may provide an additional benefit favoring PCI that will not be appreciated by these

trials. The SIRoImUS- eluting Stent (SIRIUS) study,⁸ which used a sirolimus eluting stent, has reported the largest clinical experience in diabetic patients ($n = 279$) for drug eluting stents. The target lesion revascularization rate was reduced from 22.3% (bare metal stent) to 6.9% (sirolimus stent) ($p < 0.001$). If these revascularization rates can be reproduced in routine clinical practice, it will significantly narrow the gap in revascularization rates between PCI stent and CABG.

OFF PUMP SURGERY

The CABGS have advanced with great deal advent of off pump surgery, use of all arterial conduits (IMA, radial etc.) and robotic surgery.

In contrast to earlier published trials, a recent randomized study¹² of 300 patients was unable to demonstrate any advantage with CABGS performed without cardiopulmonary bypass in terms of patient morbidity. Another randomized study¹³ of off and on pump surgery in multivessel CAD reported a lower graft patency rate at 3 months in the off pump surgery group. Yet another randomized study has reported lower long-term patency rates with radial grafts implanted during off pump surgery. The concerns raised in these recent studies need to be addressed.

WILL CABGS CONTINUE TO BE TREATMENT OF CHOICE IN MULTI VESSEL DISEASE?

It is obvious from the preceding discussion, that medical treatment and PCI can treat large number of patients with multivessel CAD. The results from several trials (RAVEL, Sirius C, Sirius E, Sirius, Taxus I, II, III, IV and several others), registries (Research) and real world practice have confirmed that DES cause significant reduction in restenosis and need for reintervention across a wide range of patient and lesion subsets.

The economics is going to play a crucial role and will influence the choice of revascularization in multi vessel disease. It is impossible to compare the short and long-term costs of PCI versus CABGS in hospitals in India. The variations are tremendous. The use of direct stenting and likely availability of DES from multiple companies are going to reduce the cost of the technology and make it more cost-effective for many Indian patients.

The ongoing studies (Arts II, comparing multivessel DES revascularization versus CABGS), (Freedom and Decode for diabetes), and several other studies should confirm the direction of wind which seems to be moving away from CABGS. The indications of CABGS are changing and this technique will be needed in patients where PCI is not feasible due to economic reasons or lesion complexity.

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