Coronary Artery Bypass Surgery vs. Percutaneous Coronary Intervention: Current Status

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Abstract
Both coronary artery bypass surgery and percutaneous interventions are competing for numero-uno position for coronary revascularisation. Though there have been significant advances in percutaneous interventions, yet they have not been perfected enough to give results equivalent to CABG in all clinical and anatomical scenarios and infact are not universally applicable also. There are guidelines, yet those are being flouted and certain ambiguities are exploited by either side to suit the procedure, not to the patient but to the doctor delivering it. This critical review thus looks at bypass surgery and PCI in light of currently available data and highlights the pitfalls in the available therapies. Certainly PCI is evolving and has come a long way and for simpler coronary anatomiies may be the preferred line of myocardial revascularisation, but certainly it has not replaced bypass surgery. The two infact should be viewed as complementary to each other with each having its niche area and domain.

Keywords: Coronary artery bypass surgery; Percutaneous coronary

Introduction
Ever since 1977 when Gruentzig performed the first percutaneous coronary angioplasty (PTCA) [1], its scope has been gradually widened. It is now being applied to more complex and multi vessel lesions. Even coronary artery bypass surgery (CABG) has seen dramatic advances since its introduction in 1967 by Favaloro [2]. Infact lately CABG has become less invasive and, notwithstanding the raging debate between off pump versus pump surgery [3], over 99% of coronary work in our centre is being performed off pump, while cardiologists are becoming more invasive. There is obviously a keen tussle between the two procedures and it's time to relook at the current status of each.

Till date all randomized controlled trials (RCTs) that have looked at CABG versus Percutaneous Interventions (PCI) have come to a common conclusion that there is no difference between the two with regard to early mortality and myocardial infarction (MI) but angina relief and rates of repeat revascularization are overwhelmingly in favour of CABG. Introduction of Drug Eluting Stents (DES) and more recently the biodegradable stents, have given further impetus to PCI with the hope that with reduction in the rates of restenosis, the latter two disadvantages of PCI would be eliminated. However, this hope is based on a faulty premise as coronary artery disease (CAD) is not a localized pathology but is segmental in nature and as against PCI, which addresses a discrete localized lesion, CABG bypasses the whole diseased segment, and therefore intuitively speaking also, CABG is likely to be more effective than PCI [4]. This prompted Spencer B King III to comment, "Five years after stent implantation almost twice as many events are related to factors other than restenosis." Infact some of these factors may be natural history-driven [5]. Let's look at some of these issues more closely.

Is Angioplasty Applicable Universally?
Angioplasty is not universally applicable and if we look at RCTs between PTCA and CABG in multivessel CAD, one finds that barely half of the patients who required revascularisation were eligible for either procedure that is PTCA or CABG. The rest of the patients were not suitable for PTCA because they either suffered from diffused atherosclerosis, multiple lesions, chronic total occlusion, calcified lesions, type C lesions, small size of the coronary vessels, severe LV dysfunction, and presence of LV clot/LV aneurysm, presence of peripheral vascular disease or other associated anomalies. In these kinds of lesions, usually PTCA is not possible but with modern technology and improvement in hardware as well as the experience gained over last decade, most of these
lesions may now be tackled, albeit with suboptimum outcomes [6]. In the pivotal SYNTAX Trial, which compared DES with CABG, 35% of patients were rejected for PTCA because of unsuitable coronary anatomy [7].

**Has the Restenosis been Eliminated?**

Though the DES have revolutionized PCI and compared to Bare Metal Stents (BMS), the restenosis rates have come down dramatically, but they are still significant. Currently accepted figures are 8.9% at 8 months with Sirolimus eluting stents (SES) [8], 7.9% at 9 months with Paclitaxel eluting stents (PES) [9] and 15.3% at 8 months with Zotarolimus eluting stents (ZES) [9,10]. The 4.7% restenosis at 8 months and improved MACE at 2 years reported in the SPIRIT III Trial [11,12], for Everolimus eluting stents (EES) was for a very limited subset of patients. Here lesions more than 28mm in length and vessel size <2.5 mm were excluded and the angiographic follow up was done in only 50% of patients [11]. Besides lesion length and lesion type (B2/C), smaller vessel size is a strong predictor of TLR [13]. Even in chronic total occlusion, the results of PCI are suboptimum. Besides technical failure (38.7% in New York PCI Registry), even if one successfully opens the artery, the binary restenosis was 22.6% for the entire treated segment in the ACROSS/TOSCA - 4 Trial with 16% incidence of stent fractures and 25% of these needing TLR within the first six months [14], besides a host of other serious complications like increased coronary perforation (RR 5.0; p< 0.001) and cardiac tamponade (RR 5.0; p< 0.01) [15].

Even the next generation Bioresorbable (BRS) stents have not tilled now achieved the desired goal. There are issues related to radial strength, dilatation range, visibility on imaging, thick struts, deliverability etc. The binary restenosis in the ABSORB Study was 12% at one year [16]; overall TLR was 45% at 12 months with Bioabsorbable magnesium stents in the PROGRESS Study [17] and 13% in the GENOUS Healing Stent Trial with antibody coated stents to capture endothelial progenitor cells [18]. Even in the ISAR TEST IV Study at 4-12 months follow up, binary restenosis was 12% with SES with disappearing polymer [19] Drug eluting balloons too have not survived the scrutiny at 9 months. In the PEPCAD III Trial, instant late loss with drug eluting balloons was 0.41, MI at 9 months 4.6%, stent thrombosis 2.0% and target vessel revascularisation (TVR) 13.8%, all of which parameters were statistically significantly higher than with DES [20].

These results have improved only marginally, if at all, over time. Raungaard et al. [21], comparing Biodegradable Polymer Versus durable Zotarolimus Eluting Stents found no difference in primary end points of mortality, MI and TLR at 12 months (5.0 Versus 5.3%). Even in ABSORB Japan Study [22] barely equivalency of results was achieved with Cobalt Chromium Everolimus Eluting Stents. To the contrary, in ABSORB III study [23] TLF was 7.8% with BRS platform as compared to 6.1% for durable platform (p=0.007). So the dream of zero restenosis has not been achieved till now. More over restenosis is not a benign event & may present as Acute Coronary Syndrome in upto two thirds of patients with increased mortality - HR 1.23; p=0.02 [24,25].

Then there is the problem of catch up restenosis [26]. This late luminal creep begins to come at around 6 months and goes on till two years, and translates into increased clinical events and TLR at 2 years of up to 24.1% with Taxus stents, 18.8% with Cypher stents and 17.4% with ISAR stents. Similar late catch up phenomenon has been reported with Xience stents at 6 and 24 months in the Spirit II Trial [27] and continues unabated with BRS platform. Intact Zhang et al. [28], in an OCT Study of ABSORB Cohort B, found edge vascular response, at both proximal and distal edges, which was progressive till at least 3 years and Cassese et al. [29,30] found late lumen loss at 6 months to be higher with BRS platform (0.30+0.59 mm) as compared to DES (0.22+0.48; p=0.035), a finding confirmed by the ABSORB II [31] - 3 year results presented at TCT meet at Washington in November 2016.

No wonder then, that 30 days readmission rates with PCI despite all the advances in stent technology, have not come down - 16.1% in 2000 and 15.4% in 2012, with 4 times higher mortality in these patients [30].

**Completeness of Revascularisation**

Tamburino et al. [32] achieved complete revascularization in only 41.7% of patients with multi vessel disease undergoing PCI with DES. They also found that complete revascularization reduced cardiac death (hazard ratio 0.37; p=0.03), death and MI (hazard ratio 0.34; p=0.008) and repeat revascularization (hazard ratio 0.45; p=0.0003) and were corroborated by Garcia et al. [33]. In SYNTAX trial [34] complete revascularization was achieved in 63.2% in CABG group as against 56.7% with PCI (p=0.005) and in the ACUITY Study [35], 60% had incomplete revascularisation following PCI with 18.7% having a residual SYNTAX Score of >18.7% translating into incrementally higher event rates proportionate to residual SYNTAX Score with each one point increase contributing to 6% increase in cardiac mortality, 2% increase in MI and 4% in TVR.

It is therefore not surprising to note that Curtis et al. [36] in their review of 3, 15, 241 patients in 1,108 hospitals performing >50 angioplasties per year, found a readmission rate of 14.6% with PCI at 30 days. One fifth of these readmissions were for acute events like MI, unstable angina, arrhythmias and heart failure and nearly 27.5% of these patients needed repeat revascularisation.

**Diabetes Mellitus & Other Co-morbidities**

Diabetic patients are altogether different ball game clinically, anatomically, etiopathologically, biologically, angiographically and rheologically. They have small caliber and diffusely diseased vessels, which are involved more distally with poor collaterals and a milieu interior of increased thrombogenicity, endothelial dysfunction and altered platelet function [37]. They also have associated co morbidities like renal dysfunction, peripheral and carotid vascular disease and pan microvascular dysfunction.

From the historical BARI Trial [38], through the ARTS [39] and Northern New England Cardiovascular Disease [40] studies, the VA Cards Study [41], Cardia Trial [42], ASCERT Study [43] to the contemporary FREEDOM Trial [44], that one groups of patients where consensus is unanimous that CABG is the preferred mode of myocardial revascularisation.

Though the use of DES [45-47] and Glycoprotein IIb IIIa inhibitors [48] have been shown to bring the restenosis rates down, Insulin treated diabetics still do less well with PCI as compared to non insulin treated diabetics [47]. In Swedish Registry [49,50], besides incomplete revascularization with PCI, Insulin dependent DM had higher restenosis (HR 1.54) and stent thrombosis (HR 1.56). When we compare the results of PCI Vs CABG, certainly CABG scores over PCI for both Non Insulin Dependent DM (HR 1.46) and Insulin dependent DM (HR 1.21), BARI 2D Study clearly showed that the
mortality and early MACE were exactly the same with CABG and PCI but CABG decreased cardiovascular event rates and CABG in insulin sensitive group fared the best (p=0.01) [51]. Even in head to head comparison between PCI and CABG in diabetics in the Cardia Trial, though the one year primary end points of mortality, MI and stroke were the same in both the groups (10.5% in CABG Group and 13.0% in the PCI group (p=0.39), revascularization was 9.9% in the PCI group Vs 2% with CABG (p=0.001) and composite MACE was 19.3% with PCI Vs 11.3% with CABG (p=0.02) [52]. In the SYNTAX Diabetes Sub study (n=452), repeat revascularization at one year with PES was 20.3% as against 6.4% with CABG (p< 0.001) [53] with an overall MACE of 26% and 14.2% respectively (p=0.0025). Besides there may be mortality benefit for CABG as shown by Tu et al. [54] and FREEDOM Study [55] - 5 yr all cause mortality 16.3% in PCI versus 10.9% in CABG (p=0.005). These results were confirmed in a number of studies [56] and meta-analyses [57,58].

Even the newer DES have not made much impression in diabetic population [59] and in SPIRIT IV [60], ENDEAVOR IV [61] and the COMPARE Trials [62] results of EES & ZES were the same as PES in diabetics though the former two had improved outcomes over PES in non diabetics. Therefore Boden and Taggart writing an editorial for the BARI 2D Trial commented, "... when revascularization is indicated, both BARI 2D and other studies support the use of CABG as the preferred approach, unless and until future studies indicate otherwise" [63].

CABG is the preferred mode of revascularisation in presence of other co-morbidities as PCI under performs in situations of chronic kidney disease [64,65], LV dysfunction [66] and Hypothyroidism [67].

**Does Surgery Confer a Survival Advantage over PCI?**

The answer to this question is a categorical ‘Yes’. It has been demonstrated quite conclusively in a number of studies that CABG gives survival advantage which PCI is not able to provide. In the SOS Trial [68] at 6 years, mortality was 10.9% with PCI, as against 6.8% with CABG, p=0.002. Even in the New York Registry data published by Hannoan et al. [69], there was statistically significant increase in both survival and MI free survival at 18 months with bypass surgery as against DES. Similar findings were reported in a propensity score matched analysis of 105,106 patients by Hitlky et al. [70], where an 8% decrease in mortality was demonstrated with CABG over PCI on a 5 year follow up. Even Trikalinos et al. [71], in a meta analysis of 61 randomized trials of PCI including 25,388 patients over a 20 years period, reported, ‘Cumulative advances in PCI have not translated into an improvement in survival or a reduction in MI’, a statement period, reported, ‘Cumulative advances in PCI have not translated into an improvement in survival or a reduction in MI’, a statement that is certainly a cause of concern, especially for patients who are either resistant or recalcitrant to usage of antiplatelet medicines. Antiplatelet resistance has been reported in 5-45% of cases and MACE increases many folds in these patients [94,95]. Diabetic subjects have a higher number of Clopidogrel non responders (p=0.04) and increased platelet reactivity leading to increased atherothrombotic risks [96]. Further 32.4% of the patients taking antplatelets experience bleeding
and 11.1% sufficient to force the individual to stop the antiplatelet medication [97], thus predisposing to late stent thrombosis. In the ADAPT-DES Study [98], those who bled had a higher mortality of 13% versus 3.2% in those, who did not (HR 5.03; p< 0.0001). Also should a person need non cardiac surgery during the first one year, and then he is faced with the difficult choice of managing bleeding versus antiplatelet medications.

DES also led to reduce collateral growth and therefore any subsequent coronary event is likely to be serious [99]. It may be for this reason that death/MI beyond 6 months was 9.1% after DES versus 3.8% with BMS (p=0.0099) at 3 years in the BASKET Trial [100].

New disease pathologies keep emerging as we follow patients longer following PCI like neoatherosclerosis [101] and vulnerable plaques, concertina effect [102] and Kounis Syndrome [103] - a continuous, chronic repetitive, hypersensitivity induced inflammation of coronaries producing acute coronary syndrome. Post PCI, OCT & IVUS have given us new insights. Seoda et al. [104] in the MGH-OCT Registry of 786 patients found incomplete stent apposition in 39.1%, stent edge dissection in 30% (only 1.4% picked up on cine angio), irregular protrusions in 53.8% and disrupted fibrous tissue in 61% patients, leading to device oriented clinical end points of 4.2% at 1 year. Stent fractures were demonstrated in 22% stents by Kan et al. [105] translating into instant restenosis (42.1%), increased TLR (24.8%) and definitive ST in 4.6%.

In BRS platform, there are additional technical difficulties due to thick struts and imaging and deliverability issues. In ABSORB II Study [106], barely 8% of BRS and 20% of Everolimus Eluting Stents had optimum device expansion with both asymmetric (p=0.007) and eccentric (p=0.004) implants leading to MACE. Similarly Gori et al. [107] demonstrated evagination in 54% BRS and periscaffold aneurysm in 4% in an OCT based study.

### Quality of Life and Cost Considerations

One has to keep in mind the social obligations that we have to our relatively impoverished society. Cost considerations cannot be ignored and DES, not only in a scenario of multi vessel CAD [108,109], but also in single vessel LAD stenosis [110,111], is not cost effective. Even in Syntax subset of patients, when quality of life and economics were analysed, it was found that at one year angina relief was much better with CABG and in patients with Syntax score of >33, CABG was cost effective. Also the follow up costs with PCI were much higher [112]. These are data for western patients and calculated according to western criteria, while in developing world, this cost consideration gets overwhelmingly weighted in favour of bypass surgery. Early short term gains of PCI get neutralized by 3 years and there was no difference in quality of life between PCI & CABG in diabetics [113].

### Long Term Safety and Performance Profile of DES

These issues are essentially subjudice and as against CABG where almost 20-30 year results are now available, we barely have five year results with evidence of late ‘catch up’ restenosis manifesting at around two years [26, 27]. Philpott et al. [114] have clearly shown that the reduced restenosis benefit of DES, present in the first year, is lost by the third year and survival between BMS and DES at 3 years is equivalent [67]. In COURAGE Trial also, early gains of PCI were lost by 3 years [115].

### Left Main Stenosis – Is it a Surgical Bastion?

Certainly not anymore! After the LE MANS Registry [116] showed improved outcomes with DES in left main, the Syntax trial has conclusively shown that in isolated left main and when associated with single vessel disease, the results of angioplasty are quite satisfactory.
[7]. Also ostial and mid shaft lesions with low Syntax Score do fairly well with angioplasty. However, distally located lesions [117] (more than 60-70%), high Syntax Score >33 [118], those associated with double or triple vessel CAD (67.5%) [7] And LV dysfunctions are still in the surgical domain [119].

PCI in distal LM has issues both when the bifurcation angle is shallow [120] and when it is steeper [121] leading to increased atherosclerosis. Restrictive bifurcation angle was an independent predictor of MACE (HR 2.65; p<0.001) even in the SYNTAX-LM Sub study [121].

MAIN COMPARE [122], PRECOMBAT [123] and other studies have shown that early events like death, MI and stroke are exactly the same between stent and CABG but repeat revascularization is much higher with stents as compared to CABG. In CREDO-KYOTO Registry [124], surgery was superior and even in matters of CVA it was equivalent to PCI at 5 years. In EXCEL Trial [125] however PCI fared better than CABG in low and intermediate SYNTAX scores with 39% reduction in mortality, MI and strokes (HR 0.61; p=0.008) at 30 days but there were higher catch up primary end points at 3 years (11.5% Vs 7.9% with CABG; p=0.02) - Ref. (Figure 1).

NOBLE Trial [126] however showed higher MACCE at 5 years with PCI (28.9%) as compared to CABG (19.1%). In a subgroup analysis of PRE COMBAT and SYNTAX Cohorts, Cavalcante et al. [127] too demonstrated 5 years MACE of 23.0% with CABG as against 28.3% with PCI (HR 1.23) mainly driven by repeat revascularisation (HR 1.85; p<0.001).

Panel shows the results of the analysis of the primary composite end point of death, stroke, or myocardial infarction at 3 years. Results of analyses of the components of the primary end point are shown in Panel B (death from any cause), Panel C (stroke), and Panel D (myocardial infarction). Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses. Hazard ratios are for the patients who underwent percutaneous coronary intervention (PCI) with everolimus-eluting stents. The rates of stroke and myocardial infarction are non-hierarchical (i.e., fatal and nonfatal events were included). In each panel, the inset shows the same data on an enlarged y axis. CABG denotes coronary-artery bypass grafting [125,128,129].

ESC/EACTS guidelines give class I (B) indication for CABG in all cases but Class I (B) for PCI only if Syntax Score is <22; Class II a (B) for Syntax Score 23-32 and Class III (B) for Syntax Scores >33. ACC/AHA guidelines are a little conservative and give Class II a (B) indication to PCI only for Syntax Score <22 and contraindicate PCI in all other situations.

CABG - Status Report

Pari Passu with advances in PCI, we have advances in CABG also. Now a days we have off pump surgery (OPCAB), non sternotomy options, day care surgery, robotics and total endoscopic CABG coming in vogue. In pump technology also, there have been major advances in myocardial preservation, in circuitry, hardware
and instrumentation. OPCAB avoids the damaging effects of cardiopulmonary bypass, thereby providing better LV protection, reduced hospital stay, reduced morbidity and mortality Ref. (Figure 2), especially in high risk patients [130] with overall reduction in the cost of surgery. OPCAB has been validated even by angiography, both early [131] and at long term, [132] though there are some concerns raised by western literature, they seem to be nullified by Lamy et al. [133] Time is not far when these procedures will be offered as day case procedures especially when totally Endoscopic & Robotically controlled CABG become a ubiquitous reality.

Pedicled LIMA - LAD graft is the gold standard with patency rates upwards of 90% at 20 years [134] and patency of RIMA, Radial Artery (RA) and Right Gastro-Epiplioic Artery (RGEA) [135] is excellent at mid to long term. Angiographic patency estimates at 5 years were 95.9% for LIMA, 91.2% for RIMA, 90.6% for RA and 81.8% for Saphenous Vein [136] Ref. (Figure 3). Comparable patencies and clinical outcomes at 5 years using alternative conduits have been validated even in the RAPCOS Trial [137].

In a meta analysis [138] looking at CABG Vs PCI for multi vessel disease, the MACE for PCI was 42.8% as against 20.8% for CABG for 5 years and repeat revascularization was 30% with PCI Vs 7.4% with CABG. Similar results have been published by Daemen et al. [139], Takagi et al. [140], Park et al. [141] and Bangalore et al. [142]. In the ACUTY Trial [143] PCI decreased bleeding, blood transfusion & acute kidney injury but at cost of increased repeat revascularisation (19.5 versus 5.2%); mortality, MI and CVA remaining neutral. However in a meta-analysis of SYNTAX and BEST Trials, Chang et al. [144] found CABG superior for mortality (HR 0.65; p<0.039); MI (HR 0.40; p<0.001) and repeat revascularisation (HR 0.55; p<0.001) and neutral for CVA (HR 1.1; p=0.714).

Total arterial revascularization (TAR) provides survival benefits unmatched by PTCA. Eight year event free survival rate was 80.2±7.3% in the experience of Angela et al. [145] and actuarial freedom from cardiac death (including hospital death) was 97.6% at 9 years with TAR [146]. Similar long term survival is a rule rather than exception with TAR. Bergsma [147] reported 7 years survival of 91%, Nishida [148] described a 7 year survival of 88% and Tavilla [149] reported a 10 year survival of 87%. Locker et al. [150] from Mayo Clinic demonstrated 8 years survival benefit for multi arterial CABG over PCI with DES (87% versus 70%; p<0.001).

Minimally Invasive CABG is establishing itself lately and provides invasiveness equivalent to PCI with improved outcomes. Holzhey et al. [151] in a large series reported an early operative mortality of 0.8%; peri-operative CVA 0.4% & early graft patency of 95.5%. Complete revascularisation was achieved in 95% patients [152]. MIDCAB too has been validated against PCI for LAD stenosis [153,154].

Also the oft heard premise that let us try PCI first and if it fails, CABG can always be offered, is not valid. PCI is not entirely benign and infact increases mortality and peri-operative complications during subsequent CABG [155].

Heart Team Concept

Though mandated as a CI I (c) indication by all guidelines, it is not implemented in true spirit for various reasons both ethical & unethical. As a consequence over 70% patients are both ill & misinformed into believing that PCI will prevent MI and increase survival [156] and barely 1% correctly understood the benefit of PCI and as a consequence nearly one thirds of patients with Class I indications for CABG are subjected to PCI [156]. Patient awareness, self regulation by physicians and strict legislation may help correct this anomaly but real disruptive game changer will be when the gate keeper role moves from a cardiologist to an imaging specialist, so that unbiased decisions are taken by a neutral authority.

Conclusion

Both PTCA and CABG have improved over the last ten years. The restenosis with DES has come down dramatically compared to BMS but is still in the range of 5-10% at 3 months and though the safety of DES has been proven, but the recurrence of angina and repeat revascularisation are still much higher than CABG. Besides that DES are costly, but to their advantage, they are patient and user friendly with early return to work and no cosmetic stigma attached. Similarly CABG too has improved and with off pump techniques, the mortality has come down to below 1% and the stroke rates too are falling to around 1%. The long term results of CABG are superior and it is cost effective, more so in scenarios of diabetes mellitus, multi vessel disease, chronic total occlusions and diffuse atherosclerosis. Therefore it is important that we combine the two technologies for the benefit of our patients and customize the treatment according to their needs. Whenever we have a simple coronary anatomy, be it single or double or triple vessel disease with a low SYNTAX score (<22 for multi vessel disease and <33 for left main disease), then angioplasty may still be considered for a patient, but if the anatomy is complex, then there is no question, CABG is the preferred choice. Both procedures are there to stay and will give good results if use for appropriate indications. Infact hybrid revascularization using Pedicled LIMA – LAD and stenting to the back of the heart arteries performed in composite operation suites may soon become the norm of the day. By the same token, one must not forget that both these procedures are palliative in nature and are likely to become obsolete at some stage, that is when either genetics takes over or some causative agent for CAD can be identified and curative pharmaco-therapeutic agent found for the same. Till such time, both will continue to exist and both will be required in a complementary fashion.

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