INTRODUCTION

Since the introduction of coronary artery bypass grafting (CABG) in 1967, and percutaneous transluminal coronary angioplasty (PTCA) 10 years later, several major clinical trials have been conducted comparing the two therapeutic strategies, such as the Bypass Angioplasty Revascularization Investigation (BARI) (1) and the Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) (2) trials. The seven-year outcome data of the BARI trial (involving 1,829 patients) demonstrated that CABG carried a significant survival benefit over PTCA and this was particularly pronounced in diabetic patients (1). In addition, nearly 60% of the patients treated with PTCA had to undergo repeat revascularization procedures and half of them relied on CABG as a subsequent therapy (1).

Nevertheless, the past two decades have witnessed a rapid progression of PTCA technology, in particular the development of intra-coronary stents. Drug-eluting stents (DES) especially, appear to have impacted significantly on the current daily practice of treating patients with coronary artery disease (3). These advances and their immediate influence on clinical practice provide a good example of how technology may shift the paradigm of medicine. Consequently, the mechanism and technique of revascularization needs to be redefined in the present era.

CABG VERSUS BARE METAL STENTS (BMS)

The endothelial response to injury during PCI may result in extensive proliferation of smooth muscle cells and extracellular matrix around the angioplasty site, leading to neointimal hyperplasia and restenosis, which in turn may result in recurrent angina and necessitate repeat revascularization (4-6). Various measures have been proposed to limit this process, such as directional atherectomy, rotabulators, or lasers. However, clinical results following these interventions have been largely disappointing as they may cause further damage to the vessel and lead to more severe neointimal hyperplasia (7-10). The use of stents following PTCA has been suggested as a method of improving the long-term outcome of PCI by reducing the incidence of restenosis and hence the need for repeat revascularization.

Several randomized controlled trials have been conducted to compare CABG and PCI-with-stent. The Arterial Revascularization Therapies Study (ARTS) (11) is one of the largest, and it evaluated the clinical outcomes of 1205 patients over a 5-year period. Although the 5-year mortality rate of the PCI group (8.0%) was comparable with that of the CABG group (7.6%), the need for repeat revascularization was far more frequent in the former group (30.3% versus 8.8%, p<0.001) (11). In terms of symptom relief, angina still presented in 21.2% of the patients after PCI, compared to a significantly lower incidence of 15.5% in the
CABG group (11). Similar findings have been reported by other investigators. The Argentine randomized trial of PCI versus CABG (ERACI-II, n=450, with a 5-year follow-up) (12) and the Medicine, Angioplasty or Surgery Study (MASS-II, n=611, with 1-year follow-up) (13) both revealed significantly higher rates of repeat revascularization in patients receiving PCI, despite similar mortality to CABG in these selected patients. Amongst all the major trials comparing stenting and surgery, the Stent or Surgery (SoS) trial was the one to report differences in mid-term (as opposed to early) survival. This trial involved 988 patients with multi-vessel disease from 11 European countries and Canada (14). In contrast to previous studies, a more than twofold increase in death in the PCI group was found at 2-year follow-up (5% in the PCI group versus 2% in the CABG group, p=0.01) (14).

Although randomized controlled trials represent “best science” in helping to determine the place of therapeutic interventions, registry data and meta-analyses are also pivotal in reflecting true efficacy of various treatments in the “real world” which involves a wider spectrum of patients. In a meta-analysis comparing CABG to PTCA with (4 studies), or without (9 studies) stents in 7,964 patients, Hoffman et al. (15) found a 1.9% absolute survival advantage favoring CABG over PTCA at 5 years, although this significance may not be maintained at 8 years. In patients with multi-vessel disease, CABG provided significant survival advantages at both 5 and 8 years (15). Patients randomized to PTCA had more repeat revascularizations at all time points; and with stents, this risk difference was still 15% at 3 years (15). In addition, patients treated with CABG also had a significantly lower risk of recurrent angina than those receiving PTCA, with a risk difference of 10% at 3 years (15).

A recent propensity analysis involving 6,033 consecutive patients over a 5-year period at the Cleveland Clinic (86% of them received CABG) indicated that in those patients with multi-vessel coronary artery disease and many other high-risk characteristics, CABG was associated with better survival than PCI with stenting after adjustment for risk profiles (16). In fact, it was found that PCI with stenting was associated with a more than twofold increase in death (hazard ratio, 2.3, p<0.0001), and this difference was observed across all categories of propensity (16). In diabetic patients (n=2,319), a higher mortality rate was observed in the PCI group and the most significant difference occurred amongst insulin-treated diabetics in which the adjusted hazard ratio reached 2.6 (95% confidence interval: 1.7-3.9) in the PCI group (16).

Treatment options for diabetic patients with CAD have always been a concern in clinical practice. As many as one third of patients receiving PCI or CABG may suffer from diabetes, as shown in the analysis of various registry data. The BARI trial has shown a sustained survival benefit of more than 20% in patients treated with CABG at 7-years, adding strong evidence that CABG should be the preferable method of revascularization in diabetic patients1. The ARTS trial also attempted to address this issue in a subgroup analysis in 211 diabetic patients, and diabetic patients in the PCI group had a higher (though statistically non-significant) 5-year mortality (13.5%) than those treated with CABG (8.3%), and a significantly higher repeat revascularization rate as would be expected considering the results of previous trials (11). Moreover, comparisons of diabetic and non-diabetic patients in this trial revealed that the diabetic ones were more likely to die when treated with PCI but not with CABG (11). This finding was echoed by the ERACI-II trial (12). A meta-analysis by Hoffman et al. (15) confirmed a significant survival benefit for CABG over PCI at 4 years but not at 6.5 years, in diabetic patients.

Another meta-analysis by Mercado et al. (17) also suggested higher (though statistically non-significant) 1-year mortality in diabetic patients after stenting. More recently, the report of the New York’s cardiac registries, which included patients undergoing CABG (n=37,212) and PCI with stenting (n=22,102) from 1997 to 2000, confirmed that risk-adjusted survival rates in the PCI group were significantly lower, whereas the repeat revascularization rate was significantly greater, than that in the CABG group at 3 years (18). In particular, the adjusted hazard ratio for the risk of death after CABG relative to PCI was 0.64 (95% confidence interval: 0.56–0.74) for patients with triple-vessel disease (18). Although without risk-stratification, Mack et al. (19) recorded lower mortality after PCI, the proportion of multivessel disease was greater in the CABG group in their database. It is noteworthy that risk-adjusted survival benefit of CABG over stenting has been repeatedly demonstrated not only in North America (15,16,18) but also in Europe (20).

The Angina With Extremely Serious Operative Mortality (AWESOME) trial was conducted to compare PCI and CABG in high-risk patients. A total of 454 patients with refractory myocardial ischemia and one
or more risk factors for adverse surgical outcome were included (21). These risk factors included prior open-heart surgery, age > 70 years, LVEF < 35%, MI within 7 days, or use of pre-revascularization intra-aortic balloon pump (21).

Variable proportions of patients received stenting in the PCI group (26% in 1995 to 88% in 1999/2000). Although survival rates in the CABG (79%) and PCI (80%) groups were not significantly different at 36 months, the need for subsequent repeat revascularization was higher in the PCI group (21). The Stenting versus Internal Mammary Artery (SIMA) study (22) compared CABG with stenting in 123 patients with proximal, isolated de novo LAD disease.

Although 2-year mortality was not particularly different, a significant and higher incidence of repeat revascularization was documented in the stent group (22). In contrast, the event-free survival rate in the ARTS trial was significantly higher after CABG than after PCI for patients with triple vessel disease (p=0.001) (11). It was acknowledged that in the ARTS trial, patients with left ventricular dysfunction, left main lesion, or concomitant hepatic or renal diseases were excluded (11). These criteria have provided a frame that may magnify the apparent efficacy of PCI. To put this in context for example, in the New York cardiac surgery registry (18), up to 24% of patients receiving CABG have an ejection fraction less than 40% – these patients are often excluded in the controlled trials yet are the very ones who are known to have a survival advantage with surgical revascularization. Excluding these sorts of patients may well unfairly reduce the potential survival benefits for surgery and introduce a favorable bias towards PCI. Hence, it must be recognized that patients in clinical trials do not necessarily accurately represent those in the “real world”.

**CABG VERSUS DRUG-ELUTING STENTS (DES)**

Although BMS implantation has significantly reduced the incidence of repeat revascularization following PCI, the rate of restenosis remains high. It was not until the emergence of DES that a true reduction in the restenosis rate following percutaneous intervention was reported and this marked a new era in PCI development. We may gain some insight into the effects of this advance in technology and its impact on treatment options by looking at trials comparing DES and BMS.

**Sirolimus – Eluting Stents (SES)**

The RAVEL Study (23) was the first randomized, double-blind trial that compared the Sirolimus-coated Cypher stent with a BMS in 238 patients with relatively simple, single de novo coronary lesions. Encouraging results were reported with an angiographic restenosis rate of 0% in the SES group and 26% in the standard stent group at 6 months (23). The 4-year results of the study also revealed sustained and significant reductions in major adverse cardiac event (MACE) and repeat target lesion revascularization (TLR) in the DES group (23).

While the RAVEL trial was criticized for the simple nature of the lesions treated, the larger Sirolimus-coated stent had been developed and a subsequent clinical trial (SIRIUS) (24) involving 1,058 patients with longer coronary lesions was instigated. The 3-year follow-up data showed a significant reduction in TLR and angiographic stenosis in the SES group (24).

The NEW-SIRIUS study, which comprised of Canadian and European data involving 452 patients also showed significant reductions in MACE at 9 months within the SES treated group (25,26). Other trials on more complicated coronary lesions have also showed positive results. These include the Sirolimus-Eluting versus Uncoated Stents for Prevention of Restenosis in Small Coronary Arteries (SES-SMART) trial (27) on small coronary vessels, and the Stenting of Coronary Arteries in Non-Stress / Benestent Disease (SCAN-DSTENT) trial (28) on bifurcation, ostial, angulated and occlusive lesions.

**Paclitaxel – Eluting Stents (PES)**

Recently, large clinical series such as TAXUS-IV (n=1,314) (29) and TAXUS-V (n=1,156) (30) have been published, and these have investigated the TAXUS slow-release stent for “longer” coronary lesions in smaller coronary vessels. Significant reductions in TLR for up to 2 years in the TAXUS-IV trial, and 1 year in the TAXUS-V trial, have been reported (29,30). The TAXUS-VI (n=446) study (31) also demonstrated a lower repeat revascularization rate following the use of the TAXUS moderate-release stent when compared to BMS.
More recent studies suggest, however, there are concerns aside from restenosis or repeat intervention following DES implantation, which may occur at a higher rate than previously thought. For instance, several groups of investigators have observed the development of subacute or late stent thrombosis (32-35). Such complications could lead to fatal myocardial infarction even a few years after DES implantation (35).

Other randomized and observational studies have documented a consistent but small increase in the absolute risk for late stent-related thrombotic events with DES.

Comparing DES (47% sirolimus-eluting, 53% paclitaxel-eluting) with BMS using data from 14 randomized trials (involving 6,675 patients) it was found that when stent thromboses occurred more than 30 days after implantation they tended to appear much later with DES than with BMS 36. In particular, the thrombosis incidence was significantly greater with DES than with BMS more than 6 months and 1 year after implantation. In another single-center observational study, 746 patients who had received 6 months of clopidogrel maintenance therapy during a 6-month randomized DES-versus-BMS trial were followed for an additional 12 months after clopidogrel discontinuation 37. The incidence of cardiac death or MI after discontinuation of clopidogrel was significantly higher with DES than with BMS (4.9% versus 1.3%), even after adjustment for potential confounders 37.

Thrombosis-related events occurred at a median of 116 days after discontinuation of clopidogrel, accounting for 25% of late events, and it tended to occur more often with DES than with BMS (37). Therefore, experts from five major professional societies recently recommend dual antiplatelet therapy for 12 months following DES implantation in patients who are not at high risk for bleeding (38).

This duration exceeds that recommended by the drug manufacturer.

In terms of implications of these factors when considering surgery or percutaneous therapy for patients the 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions have been recently reported (39).

This showed at 5-year follow-up, the death/stroke/myocardial infarction event-free survival rate was 87.1% in ARTS II SES, versus 86.0% (p = 0.1) and 81.9% (p = 0.007) in ARTS I CABG and BMS cohorts, respectively. The 5-year major adverse cardiac and cerebrovascular event (MACCE) rate in ARTS II (27.5%) was significantly higher than ARTS I CABG (21.1%, p = 0.02), and lower than in ARTS I BMS (41.5%, p < 0.001).

The cumulative incidence of definite stent thrombosis was 3.8%. Thirty-two percent (56 of 176) of major adverse cardiac events (MACE) at 5 years were related to possible, probable, or definite stent thrombosis. So it appears from this data, that at 5 years, SES has a safety record comparable to CABG and superior to BMS, but a MACCE rate that higher than in patients treated with CABG, and lower than in those treated with BMS.

Approximately one-third of the events seen with SES may be prevented through the elimination of early, late, and very late stent thrombosis.

**DISCUSSION**

With the encouraging results from various trials comparing DES and BMS, it is believed that the new technology of DES has the potential to further decrease morbidity and repeat revascularization rate in patients following PCI. However, many of the published trials were done on relatively simple coronary lesions. Even the SES-SMART, SCANDSTENT and TAXUS-V trials could not truly represent the unselected patient population routinely presented for CABG. Moreover, the longest follow-up period in the above studies was only 4 years. There have been concerns over the long-term efficacy of DES, and some authors have postulated that DES might merely be delaying, rather than reducing restenosis, since there may be stent dilapidation following total elution of the drug. It would be unwise therefore to extrapolate data comparing DES and BMS and apply the findings to a comparison of DES with CABG.

On-going clinical trials such as the Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial are primary designed to compare the 1 year outcomes of PCI with TAXUS stent and CABG in patients with triple vessel and/or left main coronary artery diseases (40). This study aims to recruit over 4,250 patients at 90 centers in Europe and the United States. Aiming at reflecting the “real world”, the study includes not
only the randomized arms but also the 2 ineligible registries and a “preference registry” (refusal treatment allocation). It will address some important issues on the relative role of DES and CABG in the treatment of patients with complex coronary artery disease, the short- and long-term cost-effectiveness as well as quality of life and its preliminary report of outcomes is discussed later. Another Future Revascularization Evaluation in patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial was also carried out to compare 5-year mortality in diabetic patients treated with either DES or CABG (37).

Obviously, more large-scale prospective studies will be needed to elucidate and define the accurate role of the currently available treatment strategies in patients with ischemic heart disease.

CABG has stood in test of time for more than 4 decades with excellent success as measured by a variety of clinical outcome markers, and patency rates of the left internal mammary artery grafted to the left anterior descending coronary artery are consistently over 90% at 10 years. The longest trial of BMS has not reached 10-year follow-up.

Moreover, as far as patient survival is concerned, no solid evidence from previous trials comparing BMS and CABG supported superiority of PCI over CABG. Registry data with much larger patient volumes have also unequivocally indicated survival benefits for patients treated with CABG in comparison to PCI for certain patient groups. It must be acknowledged that while PCI has been changing, advances in many aspects of the CABG techniques have been remarkable. As a result, CABG has been consistently regarded as “gold standard” in treating coronary disease worldwide (38).

It is apparent that CABG provides better protection against repeat revascularizations than PCI with stenting. The high rate of repeat revascularization following PCI should not be overlooked, although the use of stents has substantially reduced this, the figure still remains high (30.3% in the ARTS trial and 28.4% in the ERACI-II trial at five years). Indeed, in these two studies, a significant percentage of patients (34.7% in ARTS and 29.6% in ERACI-II), treated with PCI eventually required subsequent revascularization with CABG, a fact disguising to some extent “real” differences in reported survival rates since the trial was conducted and analyzed on an intention-to-treat principle. This high rate of repeat revascularization with the need to resort to CABG therefore questions the applicability of the survival data since up to 10.5% and 8.6% of all PCI patients eventually required CABG (11,12).

Perhaps in some ways more important than restenosis is the issue of the completeness of revascularization potentially achieved by the two treatment options? By placing grafts distal to the diseased coronary segment, CABG may deal not only with the immediate culprit lesion but the “future” culprit lesions, whereas PCI only addresses the existing target lesions (39). For this reason surgery has been considered to carry an intrinsic advantage which makes it superior to PCI irrespective of the type of stent used.

Recently, Hlatky and colleagues (41) reported a pooled analysis of individual data from almost 8000 patients enrolled in ten randomized trials of PCI and CABG over the past two decades. They conclude that, while at a median 6 years’ follow-up there was no overall difference in survival, there was a significant survival advantage with CABG in patients with diabetes (hazard ratio 0.70, 95% CI 0.56–0.87) and in those aged 65 years or older (0.82, 0.70–0.97). Furthermore, the combined endpoint of death or repeat revascularization was reduced with CABG (10%) compared with PCI (25%; 0.41, 0.37–0.45). This analysis is probably one of the most definitive and authoritative analyses of the previous randomized trials. There are problems though, however recent this analysis is in that the number of enrolled patients represented only about 5–10% of the eligible population, and the majority had single or double vessel disease with preserved LV function negating the impact of survival as an outcome comparator. A second obvious limitation is that neither the PCI nor the CABG in these trials would be considered “optimum” by contemporary standards. PCI patients did not receive drug-eluting stents and only 83% of CABG patients received an internal mammary artery, the most important prognostic factor for long-term survival after CABG and a benefit which persists long into the second decade of follow up. Additional recent evidence can also be found in the interim analyses of previously mentioned SYNTAX in 1800 patients with left-main and/or three-vessel coronary artery disease who were randomized to PCI or CABG (40).

The strength of SYNTAX is that it includes “all-comers” and patients with the most complex coronary artery disease. It also maintained a parallel registry of patients excluded from randomization (1077 in the CABG group whose disease was too complex for PCI, and 198 in the PCI group considered to be at exces-
sively high surgical risk). At 1 year (with final analyses at 5 years), 12% of patients who had CABG and 18% of those who had PCI reached the primary composite endpoint of death, myocardial infarction, stroke, or repeat revascularization. Although the difference was largely driven by repeat revascularization with no significant difference in mortality, PCI failed to reach the criteria for non-inferiority, and the authors concluded that “CABG remains the standard of care for patients with three-vessel or left main coronary artery disease”.

CONCLUSIONS

Over the past decade, the technique and outcome of both CABG and PCI have substantially advanced. Nevertheless, since majority of the clinical trials comparing the two therapeutic strategies have been limited to selected patient populations, optimal treatment modalities for high-risk patients with complex coronary lesions and multiple co-morbidities remain undetermined. Although the rapid growth of PCI industry and the consequent decline in the caseload for CABG has generated much speculation about the future role of each type of intervention, so far no valid data exist to indicate that PCI plus DES could replace CABG entirely. This opinion is largely shared by both surgeons (43,44) and cardiologists (45,46).

A contemporary summary of current opinion is for less severe coronary disease (mainly one-vessel or two-vessel disease and normal left ventricular function), there is little prognostic benefit from any intervention over optimum medical therapy. In symptomatic patients who do require intervention, there is no difference in survival with either PCI or CABG, but there is a significantly higher risk of repeat revascularization with PCI (further emphasized in a recent meta-analysis) (42). In patients with more severe coronary artery disease, and especially those with diabetes, CABG seems superior in terms of survival and freedom from reintervention. However, the recent SYNTAX data has also pointed out that PCI is a good option for patients who are ineligible for or who refuse CABG.

While applying inferences from published trials and awaiting outcomes of on-going clinical studies, we must bear in mind that patients with complex coronary disease demand safe and cost-effective treatment which provides good long-term quality of life.

Therefore, the choice of myocardial revascularization technique for an individual patient should not simply be based on the anatomical findings. Each patient should be advised by a multidisciplinary team who can present in the most balanced way the advantages and limitations of both PCI and CABG.

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