Arterial Revascularization Versus Metal Stents for Multivessel Diseases: A Shifting Frontier

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Decisions regarding the initial management of a patient with coronary artery disease are influenced by the clinical presentation, extent and severity of coronary artery disease, left ventricular function, and the associated co-morbid conditions. In 1964, Garrett et al. [1] first used coronary artery bypass grafting to treat coronary artery disease. Subsequently, the indications for coronary revascularization – CABG versus medical therapy – were the major focus of investigation in the 1970s [2–6]. These data enabled the development of comprehensive guidelines on the indications for coronary revascularization [7]. Percutaneous transluminal coronary angioplasty was introduced by Dr. Andreas Gruentzig in 1977 as a technique to treat proximal, non-calcified, simple, concentric lesions involving a single coronary artery [8]. With improvement in angioplasty equipment and technique, the use of PTCA was expanded to more complex lesions and for treatment of multivessel disease. In the mid-1980s and 1990s, the focus of investigation shifted toward the preferred method of revascularization – CABG versus percutaneous coronary interventions [9–13]. New tools were developed and new data were gathered for both technologies. Among the most significant developments in the last decade for PCI were stents and adjunctive therapy with anti-platelet agents; and for bypass surgery, the development of less invasive surgical techniques and the recognition that arterial grafts have tremendous long-term clinical benefits.

The Arterial Revascularization Therapies Study (ARTS) was a randomized, multicenter trial designed to compare the clinical outcomes between CABG and PCI *with* stenting in 1,205 patients [14]. The primary endpoints were freedom from major adverse cardiac and cerebrovascular events (death, stroke, transient ischemic attacks, non-fatal myocardial infarction, and revascularization procedures) at one year after the procedure. Patients with silent ischemia, stable or unstable angina with at least two lesions in different vessels that were potentially amenable to stent implantation or bypass surgery were included. Worldwide, 600 patients underwent stenting and 605 patients had bypass surgery.

A total of 53 patients at four medical centers in Israel were randomly assigned to undergo stenting (n=27) or CABG (n=26).

In the study reported in this issue of *IMAJ*, Eckstein et al. [15] followed the patients at the Hadassah Medical Center who met the inclusion criteria of the ARTS trial but refused to participate in the study, and compared the surgical (n=46) to the PCI (n=50) arm. At 6 months follow-up the incidence of major cardiac and cerebral events was not statistically different between both groups (11% in the stent group and 4% in the surgery group). Repeat revascularization was required in 36% in the PCI group as compared to 7% in the surgery group. However, despite the higher rate of repeat procedures in the PCI group, the quality of life was better, the total hospitalization shorter and the cost lower during the first 6 months as compared to the surgical group.

The findings reported in this article show a pattern that is similar to the ARTS trial, with similar rates of mortality and major coronary and cerebral events in both arms, and a higher rate of repeat revascularization in the PCI arm. Yet, in spite of the higher repeat revascularization rates, the overall hospitalization duration, costs, and quality of life favored PCI. While its inherent selection bias, non-randomized design and small numbers are real limitations of the study, the findings reflect the common perception of today's clinical dilemma. PCI can be performed safely in multivessel disease, but this will be offset by the higher rate of repeat revascularization procedures. The current article also claims that quality of life remains higher following PCI despite the high rate of repeat PCI. Quality of life was not different between the different arms in the ARTS trial [18].

The rate of repeat procedures in the PCI arm is relatively high in this study (37%) when compared to the ARTS data (21%). This can be explained in part by the markedly higher rate of diabetes mellitus in the current study (48%) as compared to the ARTS study (19% in the stent group). In addition, there is a major quantitative difference in the patients' angiographic characteristics and the type of revascularization between arms. In Eckstein's study, the patients

CABG = coronary artery bypass grafting
PTCA = percutaneous transluminal coronary angioplasty
PCI = percutaneous coronary interventions

in the PCI arm had a relatively large number of lesions (5.7 ± 0.8 lesions per patient) that were treated with a relatively small number of stent (1.3 ± 0.5 per patient). In the ARTS study, in the stent group the patients' average was 2.8 lesions that were treated with 2.6 stents.

The rate of arterial conduits for revascularization in the surgical group was high, with an average of 2.0 grafts per patient, almost twice the number of venous grafts (1.15 per patient). In comparison, an opposite ratio existed in the ARTS study, with only 1.1 arterial conduits per patient out of a total of 2.7 anastomoses per patient.

Therefore, to summarize, results in the PCI arm in the current study were closer to those of multivessel angioplasty studies in the late 1990s, since less than 25% of the lesions were treated with stents, whereas the surgical arm enjoyed the benefit of an aggressive arterial revascularization approach. These differences – more extensive disease, a high rate of diabetes mellitus and a low use of stents in the PCI group – explain the relatively high repeat revascularization procedures in the PCI group in the current study.

A special subgroup that may have a different course and should be addressed separately is the group of diabetic patients with multivessel diseases. Previous studies with either balloon angioplasty [16] or stents [17] have shown an improved outcome of surgery. Therefore, selection of the most adequate revascularization procedure should take into account that diabetic patients have higher rates of stent restenosis, and this may translate into different overall results as compared to non-diabetic patients. Completeness of revascularization may also be related to outcome, particularly in patients with diabetes mellitus. Nikolsky et al. [18] found that complete myocardial revascularization is associated with improved long-term (3 year) prognosis in diabetic patients with multivessel coronary artery disease treated with PCI. In the current study, the revascularization was complete in almost all patients in both arms (90% in PCI and 96% in the surgery group). In the ARTS study [19], complete revascularization was achieved in 84.1% in the surgical arm and in only 70.5% in the stent arm. At 1 year follow-up, there was no significant differences in event-free survival in surgical patients with complete vs. incomplete revascularization, however patients randomized to stents with incomplete revascularization had a lower event-free survival (69.4 vs. 76.6%) and a greater need for bypass surgery (10 vs. 2%).

Typically, the rate of progress in the field of revascularization is so fast that by the time the study is completed, including an adequate follow-up period, new methods are introduced and obviate the need for a new evaluation of more recent strategies within the different disciplines.

What has happened in the PCI discipline?

Two major developments that were not accounted for in ARTS and were not used in the current study should be considered:

- *IIb/IIIa inhibitors*: It has clearly been shown that the peri-procedural use of anti-platelet drugs increases the safety of the procedure and leads to better long-term results. This benefit was found irrespective of whether balloon PTCA [20] or stents [21] were used, and was also found in the group of diabetic patients [22]. There is little doubt today that PCI results are improved by the use of modern adjuvant pharmacotherapy.
- *Drug-eluting stents*: Drug-eluting antiproliferative stents are just around the corner. With a 6 month restenosis rate in single digit numbers (0% in RAVEL and 9% in SIRIUS, just reported at the most recent Paris Coronary Revascularization meeting in May 2002) with the rapamycin-coated stent [23], the clinical course of treated multivessel diseases will be limited mostly by the natural history of coronary artery disease. This in itself will be determined by the efficacy of both our medical therapy and the reduction of risk factors. This new approach, which will have to be carefully assessed by adequate large clinical trials, will also have to consider cost-effectiveness aspects.

What changes are expected in bypass surgery?

Bypass surgery is also in a phase of rapid transition. With the recognition that the internal mammary artery has long-term benefit, more arterial conduits are being implemented, as reflected in the current study. The arterial to venous graft ratio of 2:1 exceeds that of the ARTS trial but it is certainly the global trend today. Methods to limit myocardial and brain injury to the patient and shorten hospitalization time are being developed. Off-pump coronary artery bypass (OP-CAB), minimal invasive (MID-CAB) and percutaneous *in situ* coronary artery bypass (PI-CAB) techniques may be a way to achieve such a goal. The field of robotics is seeking its real use and dealing with learning curves and the quality of the coronary anastomosis, and new anastomosis devices are being developed to offer the surgeon better and more reliable tools.

Cost issues

With the increased awareness of treatment costs worldwide and with the growing cost of medical care, economics will play a significant role in the future. Current price levels are still in favor of PCI, according to the current study and to the cost analysis of the ARTS trial, which showed that bypass surgery exceeds stent-assisted PCI by US$ 3,000 at one year. This cost advantage in favor of stenting is present, despite additional events in the stent arm as restenosis continues to present up to 9 months after implantation. Expected additional events in the PCI arm in the current study may increase the cost of the PCI arm above the reported levels, but not the CABG arm.

The major question that needs to be answered is: how will the introduction of drug-eluting stents affect the economic balance between PCI and surgery? It is difficult to predict the cost-effectiveness of the new drug-eluting stents without adequate long-term data in patients with multivessel disease. A rough analysis shows that the acute cost will be higher with the drug-eluting stents (for a typical ARTS patient receiving three stents an incremental cost of $4,000 will occur immediately), but long-term savings due to fewer repeat procedures, which are typically required in up to 30% of patients with multivessel disease undergoing stenting, may lead to a significant reduction in the long-term cost of PCI.

There is little doubt that with the introduction of more effective devices and the reduction in price of drug-eluting stents in the next few years, a shift from metal towards drug-eluting stents will be seen worldwide for the endovascular treatment of multivessel

diseases. In the meantime, we will continue to struggle between PCI and CABG, using our best clinical judgment based on available studies conducted with older technologies. In parallel, the major frontier will be shifted to the aggressive competition between drug-eluting stents and reliable and less invasive complete arterial conduit bypass revascularization techniques.

References

1. Garrett HE, Dennis EW, DeBakey ME. Aortocoronary bypass with saphenous vein graft: seven-year follow up. *JAMA* 1973;223:792–4.
2. European Coronary Surgery Study Group. Long-term results of prospective randomized study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1982;ii:1173–80.
3. Alderman EL, Bourassa MG, Cohen LS, et al. Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. *Circulation* 1990;82:1629–46.
4. The VA Coronary Artery Bypass Surgery Cooperative Study Group. Eighteen-year follow-up in the Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery for Stable Angina. *Circulation* 1992;86:121–30.
5. Mock MB, Fisher LD, Holmes DR Jr, et al. Comparison of effects of medical and surgical therapy on survival in severe angina pectoris and two-vessel coronary artery disease with and without left ventricular dysfunction: A Coronary Artery Surgery Study Registry. *Am J Cardiol* 1988;61:1198–203.
6. Kaiser GC, Davis KB, Fisher LD, et al. Survival following coronary artery bypass grafting in patients with severe angina pectoris (CASS): an observational study. *Thorac Cardiovasc Surg* 1985;89:513–24.
7. Subcommittee on Coronary Artery Bypass Surgery. ACC/AHA guidelines and indications for coronary artery bypass graft surgery. *Circulation* 1991;83:1125.
8. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979;301:61–8
9. Rodriguez A, Boullon F, Perez-Balino N, et at. Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI): in-hospital results and I-year follow-up. *J Am Coll Cardiol* 1993;22:1060–7.
10. Hamm CW, Reimers J, Ischinger T, et al. for the German Angioplasty Bypass Surgery Investigation. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. *N Engl J Med* 1994;331:1037–43.
11. King SB, Lembo NJ, Weintraub WS, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. *N Engl J Med* 1994;331:1044–50.
12. CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularization Investigation). *Lancet* 1995;346: 1179–84.
13. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;335:217–25.
14. Serruys PW, Unger F, Sousa E, et al., for the Arterial Revascularization Therapies Study Group. Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;344:1117–24.
15. Ekstein S, Elami A, Merin G, Gotsman MS, Lotan C. Balloon angioplasty versus bypass grafting in the era of coronary stenting. *IMAJ* 2002;4: 583–9.
16. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1997;96:1761–9.
17. Abizaid A, Costa MA, Centemero M, et al. Arterial Revascularization Therapy Study Group. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. *Circulation* 2001;104(5):533–8.
18. Nikolsky E, Patil C, Roguin A, et al. Percutaneous coronary interventions in diabetic patients: the impact of complete revascularization on long-term prognosis [Abstract]. *J Am Coll Cardiol* 2002;39:47A.
19. van den Brand MJ, Rensing BJ, Morel MA, et al. The effect of completeness of revascularization on event-free survival at one year in the ARTS trial. *J Am Coll Cardiol* 2002;39:559–64.
20. Topol EJ, Califf RM, Weisman HF, et al., for the EPIC investigators. Randomized trial of coronary intervention with antibody against platelet 2b3a integrin for reduction of clinical restenosis: results at 6 months. *Lancet* 1994;343:881–6.
21. Topol EJ, Mark DB, Lincoff AM, et al. Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicentre randomised trial. EPISTENT Investigators. Evaluation of platelet IIb/IIIa inhibitor for stenting. *Lancet* 1999;354:2019–24.
22. Elezi S, Kastarti A, Pache J, et al. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. *J Am Coll Cardiol* 1998;32:1866–73.
23. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001;104: 2007–11.

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