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Will Stents of New Technology Replace Coronary Artery Bypass Surgery?

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ABBREVIATIONS AND ACRONYMS

ARTS=Arterial Revascularization
Therapy Study
CABG=coronary artery bypass grafting
CI=confidence interval
DES=drug-eluting stents
HR=hazard ratio
LAD=left anterior descending coronary
artery
LIMA=left internal mammary artery
MIDCABG=Minimally invasive direct
coronary artery bypass graft surgery
PES=paclitaxel-eluting stents
PCI=percutaneous coronary intervention
SES=sirolimus-eluting stents

KEY WORDS: *coronary angioplasty;
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ABSTRACT

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are commonly used procedures to treat patients with multi-vessel coronary artery disease requiring myocardial revascularization. In the past, several randomized comparisons between bypass surgery and coronary angioplasty were performed but had the limitation of comparing CABG to balloon angioplasty. These studies, performed in the pre-stent era, showed no significant differences in mortality and non-fatal myocardial infarction between patients treated with surgery versus PCI. Surgery had an advantage only in treated diabetic patients. More recently, in the stent era, new randomized comparisons between PCI and bypass surgery have been performed. The long-term follow-up data of the four randomized trials of PCI using bare metal stents versus CABG (Stent or Surgery trial, Artery Revascularization Therapies Study [ARTS], ERACI II, and Medicine, Angioplasty, or Surgery Study [MASS] II) showed similar incidence in the combined death, non-fatal myocardial infarction, and stroke rate with both revascularization techniques. However, contemporary treatment of coronary artery disease with stents has switched to the use of drug eluting stents. In a manner similar to the impact of bare-metal stents compared with non-stent balloon angioplasty, drug-eluting stents further reduce restenosis. Data from ARTS II support further reduction in need for repeat interventions in the stent group. During the time since these studies were initiated, CABG procedures have undergone also progressive improvement. The effects of PCI with drug-eluting stents versus minimally invasive direct coronary artery bypass surgery in the management of patients with proximal left anterior descending coronary artery stenosis were recently reported and drug-eluting stent implantation resulted in lower average number of hospital stays and similar postoperative complications. Ongoing trials should further clarify the divergent information streams in this comparison.

INTRODUCTION

The potential for multivessel percutaneous coronary intervention (PCI) to be a competitor of coronary artery bypass graft surgery (CABG) early on, led to randomized trials demonstrating equivalent survival outcomes for balloon PCI compared with CABG [1]. However, patients undergoing balloon PCI frequently required additional revascularization later on compared with CABG patients. More recently the impact of coronary stents, with their potential for more durable revascularization, has been investigated [2-6]. Data from the Arterial Revascularization Therapies Study (ARTS) trial, which randomly assigned more than 1,200 patients with multivessel disease to

bare metal stenting or CABG, demonstrated a nearly 20% absolute reduction in the need for late revascularization in the stented patients compared with earlier balloon PCI studies [7]. Overall, 1-year mortality was not different between PCI using one or more bare metal stents and CABG. However, one of the major limitations of bare metal stents is in-stent restenosis. In-stent restenosis has been recognized as very difficult to manage, with a repeat restenosis rate of 50%, regardless of the angioplasty device used [8]. Despite an exhaustive search for an effective pharmacotherapy to treat or prevent restenosis, hundreds of clinical trials have failed to identify a pharmacologic agent with proven therapeutic benefit. Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium-channel blockers, angiotensin converting enzyme inhibitors, cholesterol-lowering agents, and antioxidants, has proven almost universally negative [8].

Since approval of the first drug-eluting stent (DES), referrals for stenting have increased by more than 40%, and correspondingly, bypass surgery rates have begun to decline [9]. The early encouraging results and less invasive nature of DES coupled with the trauma involved in surgical access and conduit harvest, the systemic inflammatory response associated with cardiopulmonary bypass, the threat of postoperative neurocognitive dysfunction, and vein graft attrition has resulted in many physicians going at great lengths to avoid recommending surgical revascularization to their patients.

A great enthusiasm has been created among several interventionalists that in the future, CABG will be of limited value and applied only to selected patients not amenable to PCI. Although this may become a reality, some concerns regarding long-term efficacy and long-term safety of DES, such as late thrombosis, late stent malapposition, aneurysm formation, edge effect, need to be definitely resolved [10]. This review article evaluates current status of DES and their possible impact on the practice of coronary artery bypass surgery.

SUBSTANCES FOR DRUG-ELUTING STENTS

More than 40 substances, some that inhibit thrombotic, inflammatory, proliferative, or migratory processes and some that enhance endothelial healing, have been or are in the process of being evaluated as possible agents for DES [19,20]. Sirolimus, an immunosuppressant used in solid organ transplantation, has been found to delay endothelialization of stented surfaces. Sirolimus-eluting stents (SES) are coated with 140 µg/cm of sirolimus, which is released over either 14 or 28 days. Paclitaxel, a cancer chemotherapeutic agent used to treat ovarian and breast tumors, also has been found to delay healing processes. Paclitaxel-eluting stents (PES) are coated with 3 µg/mm of paclitaxel, which is released over at least 10 days. Both SES and PES are at present the only DES that have

FDA approval for use in de novo stenotic lesions less than 28 mm in length in native coronary arteries with reference vessel diameters between 2.5 and 3.5 mm.

RANDOMIZED CONTROLLED TRIALS OF DES

Analysis of published randomized controlled trials comparing sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES) with bare metal stents shows that restenosis rate on routine follow-up angiography was substantially lower with DES than with bare metal stents, with consequent reductions in rates of target-lesion revascularization and major adverse cardiac events [11-18]. These effects were observed with SES and polymeric PES. In general, the trials of DES with sirolimus or paclitaxel were well conducted with clinical follow-up rates of more than 90%. Follow-up quantitative coronary angiography was done in 43% to 97% of enrolled patients 6 to 9 months after the index PCI with intravascular ultrasound done in 17% to 100% patients in 7 of the 11 randomized controlled trials. Most trials were designed to assess the medium-term (6 to 12 months after index PCI) efficacy of DES at decreasing angiographic restenosis or clinical events. The inclusion criteria of all the trials specified that enrolled patients had de-novo (not restenotic) lesions in a native coronary artery with the exception of TAXUS I trial. Multilesion PCI with DES was not permitted in any trial. Patients with a recent myocardial infarction or a low ejection fraction were also excluded. Prevalence of diabetes ranged from 14% to 31%. Lesion lengths and reference-vessel diameters of the treated vessels varied between the trials, although in general the stented lesions were intermediate in length in medium-caliber vessels. The TAXI trial is the only trial to date that recruited patients representing real world interventional cardiology practice to evaluate whether a PES or an SES is superior in daily practice [19]. A total of 202 patients were included in this trial. One hundred patients received a PES and 102 received an SES. Procedural success was 99% in both groups. Incidence of major adverse cardiac events at follow-up (mean, 7±2 months) was 4% with the PES and 6% with the SES (p=0.8). The need for target lesion revascularization was very low in both groups (1% with the PES and 3% with the SES), confirming that the high success rate obtained with both stents in randomized trials can be replicated in routine clinical practice.

REAL WORLD PRACTICE OF DES

The findings from RESEARCH (Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry—the first large-scale registry of unrestricted use of SES—extend our knowledge about the clinical efficacy of SES in complex

patient subsets. Approximately 68% of patients included in the registry would have been excluded from the earlier clinical trials (eg, patients with previous coronary surgery, patients admitted with acute myocardial infarction, and those with multivessel stenting, among other high-risk characteristics). A 1-year follow-up comparative analysis of consecutive patients with de novo lesions (n=508) treated exclusively with SES and 450 patients who received bare stents in the period just before the introduction of DES revealed that patients in the SES group more frequently had multivessel disease, more type C lesions, received more stents, and had more bifurcation stenting [20]. At 1 year, the cumulative rate of major adverse cardiac events (death, myocardial infarction, or target vessel revascularization) was 9.7% in the SES group and 14.8% in the pre-SES group (hazard ratio [HR], 0.62, 95% confidence interval [CI]: 0.44 to 0.89; p=0.008). The 1-year risk of clinically driven target vessel revascularization in the SES group and in the pre-SES group was 3.7% versus 10.9%, respectively (HR, 0.35, 95% CI: 0.21 to 0.57; p=0.001). In three separate reports, RESEARCH investigators have shown DES implantation as highly effective for focal in-stent restenosis [21] and a promising and safe strategy for left main coronary artery lesions [22] and for patients with ST-elevation acute myocardial infarction [23]. More importantly, RESEARCH registry provides unique insights into the technical aspects of stent deployment techniques. Implantation of SES was always performed at high pressures (more than 12 atmospheres), and post-dilatation was liberally performed to achieve optimum angiographic results. Care was taken to avoid vessel injury beyond the stented area, and post-dilatation was performed with balloons shorter than the stent length. The number of stents, the total stented length, and the utilization of longer stents were higher in the SES group than in the bare stent group, which reflects an attempt of the operators to avoid geographical miss and cover the entire diseased segment with the DES (ie, “from normal tissue to normal tissue”)—the “longer is better” philosophy.

IMPACT OF DES ON VOLUME OF CORONARY ARTERY BYPASS SURGERY

Treatment choices and treatment patterns for coronary artery disease have changed over the past several years, and are likely to evolve further in the next few years. Since the emergence of encouraging short-term and midterm outcomes of DES from randomized controlled trials and real world registries, there has been much discussion in the cardiovascular community regarding the potential impact of this revolutionary new technology on coronary bypass surgery volume. Many cardiologists and physicians have become reluctant to recommend surgical revascularization in the present era

of DES partly from the fact that CABG is associated with a high up-front mortality and significant morbidity. However, in experienced centers available data indicate that mortality for isolated CABG should range from 1.2% to 1.7% [24]. At the same time, recent advances in the form of off-pump coronary artery bypass surgery and MIDCABG have significantly reduced the morbidity associated with CABG [25]. It is generally accepted that left internal mammary artery (LIMA) to left anterior descending coronary artery (LAD) grafts are a durable and effective treatment for coronary artery disease with 95% of these grafts being widely patent 10 years after their construction, and that their successful construction confers a survival benefit on the patient [26].

Despite these improved results, the expanding use of DES is expected to have a negative impact on CABG surgery volume. Some of this negative impact will be undoubtedly due to the simultaneous availability of effective medical therapy for what is clearly a chronic disease.

To date, results of only one randomised controlled trial comparing DES with minimally invasive direct coronary artery bypass graft surgery (MIDCABG) in patients with LAD stenosis have been published [17]. In this trial symptomatic patients (n=189), with an isolated high-grade lesion (stenosis of >70% of the luminal diameter) in the proximal LAD coronary artery (from the ostium to the first diagonal branch), were randomly assigned to the DES group (n=119) and the MIDCABG group (n=70). During the 6-month follow-up period, 1.7% (n=2) in the DES group needed repeated revascularization procedures for target lesion revascularization compared with 5.9% (n=4) in the MIDCABG group (p=0.196). The rates of death and myocardial infarction were similar in both groups (DES 0.0% [n=0] versus MIDCABG 2.9% [n=2], p=0.135; DES 1.7% [n=2] versus MIDCABG 2.9% [n=2], p=0.627; respectively) during 6 months of follow-up. In-hospital length of stay was significantly shorter in the DES group compared with the MIDCABG group (5.8±2.1 days versus 8.9±2.6 days; p=0.001). Implantation of DES and MIDCABG surgery showed similar rates of myocardial infarction, the need for repeated revascularization, and death during 6 months of follow-up. However, DES implantation resulted in lower average number of hospital stays and similar postoperative complications.

ARTS II study, which was designed to assess the efficacy of the SES in patients (n=607) with multivessel coronary artery disease compared with those of the surgical (n=605) and PCI (n=600) arm of the ARTS I study, as measured by major adverse cardiac and cerebrovascular event-free survival at 1 year, provided us a better comparison of DES and CABG. The one year survival rate was 99% and the composite endpoint of MACCE-free survival 89.5% which approached the results of surgery in ARTS I.

The results of new randomised trials will further clarify the optimal method for treating patients with multi-vessel disease

in the era of DES. The FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multi-vessel Disease) trial is an international, multi-center ongoing trial that randomly assigned 2,400 patients with multi-vessel coronary disease and diabetes mellitus to bypass surgery or SES implantation. The patients will be followed up for 5 years. The SYNTAX (SYnergy Between PCI with TAXUS and Cardiac Surgery) study has been designed to randomize approximately 1,500 patients with three-vessel disease or left main disease, or both, to bypass surgery or multi-vessel PCI with the TAXUS stent.

A parallel registry for patients not enrolled is also planned for both studies. Hopefully, these trials will provide important information to guide the choice of the optimal revascularization strategy for patients with multi-vessel disease.

POTENTIAL DRAWBACKS, CONCERNS, AND UNRESOLVED ISSUES RELATED TO DES

The enthusiasm over DES is nearly universal among interventional cardiologists, and the promise of the virtual elimination of restenosis may force us to redefine the practice of cardiology. However, there are some drawbacks such as the late “catch-up” phenomenon, or stent thrombosis. A valid concern is that in the attempt to reduce restenosis further to near zero, it is most important to consider also safety issues first [27-29]. Whereas restenosis has not been shown to be the major contributor to survival, the complications of acute vessel closure markedly reduce the long-term survival of patients. Therefore, any efforts to control restenosis, by modifying stent deployment techniques, must be balanced by an avoidance of any increase in complication rates. Another important issue is the cost for the unrestricted use of DES as an alternative to CABG.

IMPLICATIONS OF INCREASING DES USE FOR CARDIAC SURGERY

Cardiac surgeons must be aware of the potential risk of increased postoperative bleeding in this high-risk group of patients all of whom receive anticoagulation and antiplatelet medication during PCI. Modification of surgical techniques such as avoiding cardiopulmonary bypass and performing myocardial revascularization off-pump in patients who have received anticoagulants such as clopidogrel may theoretically reduce the incidence of postoperative bleeding and reduce the morbidity associated with need for re-exploration and transfusion of blood products.

In these rapidly changing times of catheter-based coronary interventions perhaps integrated (“hybrid”) coronary revascu-

larization of patients with multi-vessel coronary artery disease may be an alternative approach. This combined procedure is believed to offer the best of both worlds, MIDCABG and DES.

CONCLUSIONS

Despite our excitement about DES, we must remember that symptomatic atherosclerosis will be treated adequately with DES but not cured. If CABG ends up in the textbook of outdated procedures, in all likelihood it will be not only because of advances in interventional cardiology but also in the understanding and prevention of atherosclerosis. For now as well as the near future, it will perhaps be more prudent to look at DES and CABG as complementary therapies rather than rival techniques for myocardial revascularization.

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