Drug-Eluting Stents

Cost Versus Clinical Benefit
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The publication in January 2001 of the first-in-man results showing zero restenosis after sirolimus-eluting stent implantation produced enormous excitement in the cardiological community. The long-awaited tool—a safe, restenosis-proof, easy-to-use stent—had been found. It was not too long thereafter that paclitaxel-eluting stents also demonstrated their capability to decrease restenosis. Today, both sirolimus- and paclitaxel-eluting stents have been shown in randomized trials to reduce restenosis as compared with conventional metallic stents (Figure 1). Most of these studies have been recently released in the form of abstracts during medical meetings and are still unpublished. In addition to sirolimus and paclitaxel, other agents have shown promising early results in recent studies, enlarging the body of evidence demonstrating the potential benefits of what are known as drug-eluting stents. Regulatory agencies have been very active in evaluating some of these devices in the United States, Europe, South America, and Asia. The sirolimus-eluting stent has been available for routine use in Europe, South America, and Asia since the first half of 2002 and received approval from the US Food and Drug Administration to be marketed in April 2003. Paclitaxel-eluting stents have also received CE (Conformité Européenne) marking for commercialization in Europe and are now beginning to be commercialized.

The case seemed to be closed. Restenosis, the Achilles’ heel of percutaneous revascularization, appeared defeated. However, since the sirolimus-eluting stents became available, very little has changed in the everyday life of almost all interventional laboratories in Europe. Why? Has the new treatment presented any undesirable effect? Was the desire to defeat restenosis not as great as supposed? The answer is none of the above. The limitation currently impeding more widespread use of the new technology is nontechnical, nonmedical, and nonbiological. The list price of the sirolimus-eluting stent in Europe is €2300 ($2500 US). This high price relative to bare stents, as well as the absence of incremental reimbursement in most countries, has been an obstacle to more widespread utilization of drug-eluting stents.

Restenosis: The Problem
Coronary restenosis has long been considered the main limitation hampering the efficacy of percutaneous revascularization. Although stent implantation has been shown to reduce restenosis in vessels with reference diameter ≥3.0 mm, as compared with balloon angioplasty, in-stent restenosis still occurs in 10% to 40% of the patients. In the last 3 decades, a great deal of money and effort has been expended evaluating an endless list of failed concepts, strategies, devices, and drugs to decrease restenosis. But is in-stent restenosis really so bad?

The occurrence of restenosis remains largely unpredictable for any particular patient, although powerful predictors of restenosis have been described that are helpful to characterize a population of patients. Furthermore, in-stent restenosis has a high recurrence rate. In its most complex forms, repeat restenosis may occur in up to 50% to 80% after redilatation with balloon, rotablator, or laser. Brachytherapy has been demonstrated to reduce the incidence of repeat restenosis. However, the use of brachytherapy has been restricted to a relatively small number of centers. The need for a multidisciplinary approach, with addition of radiation oncologists and...
angina or death,8 as in the natural history of unstable patients with de novo lesions. Instead, refractory angina pectoris is the main complication of untreated restenosis. The lack of any effect of restenosis on mortality is readily appreciated by the comparison of angioplasty versus surgery.9 In most randomized trials, death and myocardial infarction rates were virtually identical between the 2 treatment modalities (eg, surgery or medical). Similarly, sirolimus-eluting stents markedly reduced restenosis for patients at both extremes of the risk spectrum. Nondiabetics with short lesions (<12 mm) and large vessels (≥30 mm) had an 81.7% risk reduction of in-segment restenosis, whereas patients at the highest risk (diabetics with longer lesions [≥15 mm] and small vessels [<2.5 mm]) had a significant 64.5% decrease in the risk of restenosis. Similarly, in the RAVEL trial,11 patients with vessel size <2.36 mm (one third of the population) presented with the same rate of binary restenosis (ie, no restenosis) as patients in the upper tertile (reference diameter >2.84). Recently, sirolimus-eluting stents have shown promising results for the treatment of in-stent restenosis in a series of 25 patients with relatively simple lesions (4% binary restenosis rate at 1 year).12 Sirolimus-eluting stents have also been evaluated for highly complex patients with in-stent restenosis. In an initial experience with 16 patients (including 50% with multiple previous interventions, 44% needing implantation of ≥36-mm sirolimus-eluting stents, 25% with failed brachytherapy, 19% with total occlusions, and 6% with transplant vasculopathy), the binary restenosis rate at 4 months was 20% and the death rate was 12.5% at 9 months.13

Non-polymer–coated paclitaxel-eluting stents have been shown to reduce binary angiographic restenosis in the European evaLUation of a Taxol-Eluting Stent trial (ELUTES)3 and the ASian Paclitaxel-Eluting stent Clinical Trial (ASPECT).4 In these studies, non-polymer paclitaxel stents (high-dose formulation) were associated with 3% and 4% binary angiographic restenosis rates, respectively, versus 21% and 27% in bare stent controls.3,4 Polymer-covered paclitaxel-eluting stents have been evaluated in the multicenter, randomized treatment of de novo coronary disease using a single paclitAXel-elUting Stent trial-II (TAXUS II).6 In this study, the incidence of in-segment restenosis at 6 months was reduced from 20% and 24% in the bare stent group to 6% and 9% in the slow- and moderate-release paclitaxel stent formulations, respectively. However, when patients treated only with the study stent were analyzed, single, noncomplex de novo lesions, the rate of binary angiographic restenosis (diameter stenosis >50%) after sirolimus-eluting stent implantation was zero at 2 years and at 6 months, respectively. The efficacy of sirolimus-eluting stents was confirmed in the subsequent multicenter randomized double-blind study of the sirolimus-coated Bx Velocity stent in the treatment of patients with de novo coronary artery lesions (SIRolImUS-eluting Bx velocity balloon expandable stent trial; SIRIUS). In this study, in-stent binary restenosis (within the stented portion and the 5-mm segments proximal and distal to the stent) were reduced by 75% (8.9% versus 36.3%; \( P<0.01 \)).5 In the SIRIUS trial, long lesion length, small reference vessel size, and diabetes were shown to be independent predictors of increased risk of restenosis (in stent and segment), in patients treated either with sirolimus-eluting stents or with bare stents. However, sirolimus-eluting stents markedly reduced restenosis for patients at both extremes of the risk spectrum. Nondiabetics with short lesions (<12 mm) and large vessels (≥30 mm) had an 81.7% risk reduction of in-segment restenosis, whereas patients at the highest risk (diabetics with longer lesions [≥15 mm] and small vessels [<2.5 mm]) had a significant 64.5% decrease in the risk of restenosis. Similarly, in the RAVEL trial,11 patients with vessel size <2.36 mm (one third of the population) presented with the same rate of binary restenosis (ie, no restenosis) as patients in the upper tertile (reference diameter >2.84). Recently, sirolimus-eluting stents have shown promising results for the treatment of in-stent restenosis in a series of 25 patients with relatively simple lesions (4% binary restenosis rate at 1 year).12 Sirolimus-eluting stents have also been evaluated for highly complex patients with in-stent restenosis. In an initial experience with 16 patients (including 50% with multiple previous interventions, 44% needing implantation of ≥36-mm sirolimus-eluting stents, 25% with failed brachytherapy, 19% with total occlusions, and 6% with transplant vasculopathy), the binary restenosis rate at 4 months was 20% and the death rate was 12.5% at 9 months.13

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restenosis was observed in only 2% in the slow-release and 1% in the moderate-release paclitaxel stents. These results confirmed the previous findings of the smaller TAXUS I trial, in which patients treated with the slow-release polymer-covered paclitaxel stents showed no restenosis, as compared with 10% in the control group.

**Drug-Eluting Stents: Where Are the Side Effects?**

In 2 recent reports from the same series of patients, Liistro et al. and Virmani et al. have described a late catch-up phenomenon after implantation of a high-dose (800-μg) paclitaxel-derivative QP2-eluting stent. The restenosis rate was 13% at 6 months and 62% at 12 months. Histological analysis showed signs of delayed healing with active inflammation still present at 1 year. However, the authors emphasized that "potential problems such as the non-erodable thick polymer sleeve, very high concentration of the active drug, extended release kinetics, open stent architecture, and inhomogeneous drug delivery (possibly affected by the interspace polymer sleeve) may have compromised the performance of the QuaDS-QP2 stent" and concluded that "...the overall clinical success of any drug-eluting stent may be dependent on multiple design factors and not the drug alone."

Short-term as well as long-term efficacy should be evaluated separately for each drug-eluting stent, given that a "class effect" is unlikely to occur because of the myriad possible variations in the complex metallic platform/polymer (or not)/pharmacologic agent. Indeed, a number of drug-eluting stents have already been proven ineffective in reducing restenosis, with even worse results being reported, as compared with conventional bare stent. To date, the sirolimus-eluting stent has the largest body of data and longest period of follow-up. The first-in-man study has shown persistent positive results up to 2 and 3 years, without any evidence of late catch-up restenosis. In the RAVEL trial, no further events due to restenosis were observed between 6 months and 1 year. With paclitaxel, no rebound effect was seen from 6 to 12 months in the TAXUS I, ELUTES, and ASPECT trials.

Obviously, a very delayed loss of the initial benefit, for instance after 3–4 years, cannot yet be ruled out. However, in this hypothetical setting, should a repeat intervention after 3 years be viewed as a therapeutic failure? In a recent analysis of surgically treated patients with multivessel disease included in the Bypass Angioplasty Revascularization Investigation (BARI), significant stenoses were detected after 4 years in 10% to 15% of internal mammary grafts and 25% to 30% of saphenous vein bypass grafts. It seems clear that a meaningful comparison between the results of treating multivessel disease with drug-eluting stents versus surgical revascularization will need an extended period of follow-up to fully assess the differences (or similarities) in outcomes with the 2 strategies.

In the first-in-man and RAVEL trials, no binary angiographic restenosis was observed. However, in the subsequent SIRIUS trial, restenosis (in-segment) did occur in ~9% of the cases. Indeed, in diabetics with small vessels and long lesions, in-segment restenosis was observed in 23.7% of cases. Does this mean that sirolimus-eluting stents are not restenosis proof? The populations treated in the first-in-man and RAVEL trials (no restenosis) and in the SIRIUS trials (some restenosis) were significantly different in terms of their intrinsic risk of restenosis. SIRIUS included patients with a higher risk profile and more complex lesion anatomy. It seems logical to assume that these differences in baseline characteristics could justify, at least in part, the differences in outcomes between the 2 studies. However, if so, what would be the performance of the new device in the real world, where complex cases are the rule? In everyday practice, will the effects still be worth the cost of the new treatment? To evaluate this question, the sirolimus-eluting stent has been used as the device of choice for every percutaneous intervention in Rotterdam since April 2002, as part of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry. Patients were treated without clinical or anatomic restriction, and the incidence of major adverse cardiac events is to be evaluated (defined as death, nonfatal myocardial infarction, or repeat revascularization). In this study, sirolimus-eluting stent implantation was observed to be safe in patients with acute coronary syndromes, with a 30-day major adverse cardiac event rate similar to that of a control group treated with bare stents (6.1% versus 6.6% respectively; P=0.8). In a preliminary analysis of the 6-month outcomes of the first 280 patients enrolled, including patients with multivessel stenting, acute myocardial infarctions, total occlusions, bifurcation lesions, and in-stent restenosis, the incidences of target vessel revascularization and major adverse cardiac events were 2.9% and 6.7% respectively. Although promising, these preliminary long-term results must be interpreted with caution until final results are available.

In the RAVEL trial, stent malapposition (as observed by intravascular ultrasound) was more frequent at 6 months in sirolimus-eluting stent patients than in the control arm. Moreover, in SIRIUS, late acquired stent malapposition was more commonly observed in the sirolimus group. However, in TAXUS II patients treated with bare stents or with paclitaxel-eluting stents, there were similar rates of late-acquired malapposition. Nevertheless, these ultrasound observations of late malapposition have not been associated with any adverse events throughout the follow-up period in any of these studies.

**Drug-Eluting Stents: The Costs**

Developmental and research costs, acquisition of exclusive and expensive licenses from pharmaceutical companies, building of new manufacturing facilities, and low production yield in the early stages of the new product are all cited as reasons to explain the high cost of drug-eluting stents.
However, at the present stage, the real economic value of drug-eluting stents is still unclear, as is the profit made by the leading industries manufacturing these devices. In an analysis from the RAVEL trial (B.A. van Hout, PhD, Academic Medical Center Utrecht, Julius Center, Utrecht, the Netherlands, personal communication, October 2002), the utilization of the sirolimus-eluting stent resulted in a mean additional procedural cost of €1286, as compared with the control group based on costs in the Netherlands. However, because of the decrease in reinterventions attributable to the sirolimus-eluting stent at the end of the first year of follow-up, the estimated cost difference had decreased to €54. In other words, in the RAVEL trial, the reduction of major event risk from 28.8% to 5.8% after placement of the sirolimus-eluting stent was accomplished at an extra cost of €54 per patient. To account for the so-called oculostenotic reflex that could have artificially increased the rate of reinterventions because of the protocol-mandated angiographic follow-up, both costs and effects were corrected on the basis of the data from the BElgium NEtherlands STENT II (BENESTENT II) study. In this analysis, after 1 year the adjusted event rates were 16.9% and 5.8% in the bare and sirolimus groups, respectively, and the sirolimus-eluting stent was associated with an additional cost of €166 per patient. The balance between costs and effects seemed highly attractive (Figure 2), with a minimal increase in costs for an $\approx 60\%$ risk reduction in the worst-case scenario. For comparison, previous studies evaluating the anti-restenotic effect of conventional stents have shown “only” a $30\%$ risk reduction of adverse event as compared with balloon dilatation, at an additional cost after 1 year of $\approx \$10000$ US per case.$^{22}$

The cost and effect estimations derived from the RAVEL trial cannot be directly extrapolated to other situations. In this study, only simple lesions were treated with implantation of a single stent, and the late target lesion revascularization was zero. The balance between costs and effects in more complex situations, in which restenosis may occur in a small but sizable number of patients, has to be specifically analyzed. Furthermore, the number of stents used per procedure may markedly increase procedural costs, potentially limiting the use of this new technology for the treatment of multivessel disease. It is estimated that $\approx 1 000 000$ percutaneous interventions are performed each year in the United States, and $\approx 80\%$ of these patients receive stents. Assuming a 100% usage of drug-eluting stent, at a rate of 1.5 stents per patient and a potential $\$2000$ US difference between drug-eluting and bare stents, an extra $\$2.4$ billion would be added in procedural costs per year. With a 15% reduction in reinterventions (at a cost of $\$10 000$ to $\$12 000$ per procedure for repeat percutaneous coronary procedure and $\$20 000$ to $\$30 000$ per procedure for coronary bypass surgery), the cost offset with unrestricted usage of drug-eluting stents in the patients at present receiving bare metal stents would be $\approx \$1.5$ billion each year. However, if there is any substantial movement from coronary bypass surgery to drug-eluting stents, additional savings from avoiding the high cost of bypass surgery could potentially result in an attenuation of net costs for payors. Nevertheless, although potentially cost effective in reducing repeat revascularization, it is clear that utilization of drug–eluting stents will require a redistribution of budgets and priorities in the health system as a whole, with a shift of an enormous amount of money to manufacturers. This phenomenon is likely to be repeated with the introduction of other new technologies that can replace open surgical procedures with less invasive, technologically driven procedures and will continue to present a challenge for the foreseeable future.

Historically, all relevant technological innovation in interventional cardiology has been incorporated into clinical practice. Today, an arsenal of multiple types of guiding catheters, new-generation contrast agents, steerable guidewires, adjunctive medications, intracoronary diagnostic tools, dilatation devices, distal protection devices, and access closure devices encompass the armamentarium of what has been named percutaneous intervention, only vaguely resembling the first days of coronary angioplasty. The speed with which new technologies are integrated over time seems to be dependent on their efficacy, safety, and economic factors and varies from country to country. Curiously, as performed in the late 1980s in Europe, balloon angioplasty was associated with a procedural cost of $\approx \$4300$ US,$^{23}$ whereas in the mid-1990s, coronary stenting was performed at a cost of $\approx \$4400$ US.$^{22}$ History has shown that an outsider (i.e., a company not belonging to the leading corporations) may unexpectedly introduce a competitive and successful product with a lower price so that the major companies are compelled to reduce the price of their own products, triggering an overall lowering of the costs. We foresee that some of the manufacturers of new eluting-stent designs may purposely target the non-US market with lower regulatory barriers as a "profit-
able” field of expansion, so that the non-US patient in Europe, South America, Far East, and Africa may soon benefit from a low-priced, non–Food and Drug Administration-approved drug-eluting stent.

Conclusions

By dramatically decreasing the rate of restenosis, drug-eluting stents constitute one of the most important advances in interventional cardiology. However, at present, cost constraints and lack of incremental reimbursement have limited their utilization in daily practice in many countries, although initial analyses of the sirolimus-eluting stent have shown a highly favorable cost-effectiveness profile in reducing repeat revascularization and combined major cardiac events. A more comprehensive understanding of the impact of the new treatment in a wide variety of patients, as well as market competition with changes in the cost of these devices, is likely to redefine the relationship between costs and benefits.

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References

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