Review Article

Cost-Effectiveness of Drug-Eluting Stents

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It is widely known that the main drawback of the non-surgical treatment of coronary artery disease with either balloon angioplasty or stent implantation is restenosis of the treated lesions, leading to recurrence of the symptoms and worsening of the quality of life.[1-4] This phenomenon is a typical healing process in response to the vessel trauma and consists of elastic recoil of the dilated artery and neo-intimal proliferation, which is a biological response to the mechanical injury.[5-8] The rate of angiographic restenosis after bare metal stent implantation varies from less than 5% to over 50% depending on the different clinical and anatomical features of the patients treated, leading to a rate of clinical restenosis and need for a new revascularisation procedure of 4% to 30%.[5-7,9,10]

Drug eluting stents (DES) represent one of the most important developments in interventional cardiology (along with balloon angioplasty and metallic stent development) and have brought about a dramatic change in the treatment of coronary artery disease.[11-16] DES bring together an antiproliferative drug to prevent excessive neo-intimal formation, a drug delivery system to release the active drug at a specific rate, and a stent to carry both the drug and the drug delivery system and to act as a mechanical scaffolding device. DES combine different stent platforms with various drugs and/or polymers with different elution rates and actions. DES with CE approval include the sirolimus (CYPHER™, Cordis J & J), pacli-

taxel (TAXUS™, Boston Scientific), zotarolimus (ENDEAVOR™, Medtronic), tacrolimus (JANUS™, Sorin), and everolimus (XCIENCE™, Guidant) eluting stents. It is worth noting that many more additional drug-eluting stents are expected to be available in the near future. DES have been extensively investigated in the form of the sirolimus-eluting stent (SES) and the paclitaxel-eluting stent (PES).[14,17-20]

Implantation of these devices, compared to bare metal stents (BMS), has led to a dramatic decrease in restenosis rate in the pivotal clinical trials as well as the large randomised studies performed throughout the world, indicating that the risk of restenosis can be reduced by 49% to 81% when DES are used to treat the *de novo* and relatively non-complex lesions which were included in these trials.[14,17-20] In addition, DES superiority over BMS has been definitively documented in "real world" populations.[14,21-25] More recently, data from the T-SEARCH registry and ARTS II study, which included patient subsets with more complex and higher restenosis-risk lesions, confirmed the improved results of DES compared with BMS and showed for the first time a non-inferiority of percutaneous coronary intervention (PCI) with DES implantation to coronary artery bypass grafting (CABG) in the treatment of patients with multi-vessel coronary artery disease.[11,21,23,25-31] As a result, from the clinical point of view, the introduction of DES has allowed physicians to treat patients with more complex

and high-risk lesions, such as diabetics or patients with long lesions in relatively small vessels, proximal location and total occlusions, who were previously treated with CABG,[11,21,23,25-27,29,32] expanding the total number of the procedures as well as the total financial impact of the non-surgical treatment.

Although the clinical benefits of DES usage are increasingly evident, important concerns about their cost have been raised in the medical community.[33-37] The increased cost of a DES is the final result of the higher research and development costs of the manufacturing companies, expenditure for the acquisition of exclusive and valuable licenses from pharmaceutical companies, the need for new manufacturing facilities for new designs and the relative low production levels. Generally, the price of a DES is at least three times higher than the price of a conventional BMS and most authors report implantation of 1.5-2 stents per patient treated, leading to a significant increase in the initial total cost of the procedure. Lemos et al suggested that the unrestricted use of DES in all USA patients who currently receive standard BMS would cost the system about $1.5 billion each year.[38] Moreover, Greenberg et al estimated that uniform conversion of all current standard BMS procedures to DES would result in a initial cost increase of about $2800 per patient treated.[39] Consequently, the great economic impact on healthcare budgets associated with the extensive use of DES remains a crucial issue, affecting worldwide socioeconomic policy.

Issues concerning the cost-effectiveness of DES include questions about the impact of DES implantation on "hard clinical" endpoints such as death or re-infarction, reduction of post-PCI restenosis rate in real world practice, and special patient subsets; the impact of DES on the need for CABG, either as a primary procedure or during the post-PCI follow-up period; the long-term effectiveness of DES in treating coronary artery disease patients; and both the short- and long-term safety of these devices.[14,39]

The main concern arises from the fact that DES use does not affect mortality following PCI procedures. All the available data show no influence of DES implantation on mortality rate following the procedure, when compared to BMS.[14,40] Indeed, a combined analysis of the TAXUS II, IV, V, VI clinical trials showed no difference in survival rate during a follow-up period of two years between patients receiving TAXUS™ stents or control BMS (97.7% versus 97.6%, respectively). Similarly, a pooled analysis of 4 clinical trials (SIRIUS, E-SIRIUS, C-SIRIUS and RAVEL) using

CYPHER™ stents in 1748 patients again showed no difference in mortality rate, during a follow-up period of 2.5 years, between patients who were treated with DES or control BMS (4.1% versus 3.0%, respectively). In addition, in a meta-analysis of DES randomised trials, Babapulle et al showed that DES usage had no impact on mortality or myocardial infarction rate in comparison to BMS.[41] On the other hand, the main effect of DES implantation, namely the reduction of restenosis rate, is a secondary outcome and to date no study has demonstrated a definite link between restenosis and mortality, except for one report of BMS use in mostly diabetic patients.[42-44] Consequently, despite the clear clinical benefits, concerns remain as to whether the additional cost associated with the reduction or even elimination of restenosis is worth paying.

What relevance, if any, do the results of non-DES versus CABG trials have in the DES era in regard to multi-vessel disease? And what role should economic considerations play when comparing therapies? Recent studies addressed the economic impact and the money saving result of revascularisation performed with DES versus non-DES.[38] These data underscore the non-inferiority of DES PCI to CABG, with the clinical implication that many patients and physicians are led to select PCI with DES implantation as the primary treatment option for multi-vessel coronary artery disease (CAD), rather than CABG. Moreover, the decreased need for re-interventions, due to lower rates of restenosis and target lesion revascularisation among patients treated with DES implantation, definitely leads to a lower need for CABG after DES PCI compared to BMS PCI. Furthermore, it has been hypothesised that, given the approximate 7% frequency of in-hospital vein graft occlusion, DES may in fact be a more durable means of coronary revascularisation than CABG using grafts. On the basis of the ARTS II trial results, it seems likely that DES will result in similar reductions in the setting of multi-vessel PCI and thus in abolition of the difference in repeat revascularisation between CABG and stenting.[38,45]

The economic impact of a strategy of multi-vessel stenting with DES could be profound. In contrast, it has been reported that the US hospitals lose money if more than 1.43 Cypher stents per patient (with only 50% DES utilisation) are implanted during a single PCI procedure.[45] Therefore, it is over-simplistic to assume that the reduced frequencies of target lesion restenosis with the adoption of DES would favourably influence the relative costs of PCI versus CABG. The comparative efficacy of these devices in relation to

bypass surgery will be shown when the results of the mega trials FREEDOM and SYNTAX are published.

Stent thromboses have been a lingering question within the cardiology community. However, it must be emphasised that from the randomised controlled trials, the corresponding meta-analyses, and the registry data in higher risk populations, the rates of early (acute and subacute) thrombosis seen with DES awarded with CE marking approximate the rates of BMS. However, recent registry data suggest that the rate of late thrombosis in real-life situations is higher.[46] In this registry, the most important predictor of late stent thrombosis was the cessation of antiplatelet therapy. Therefore, patients may not be as compliant with antiplatelet therapy in actual practice as they are in clinical trials, potentially leading to a higher number of events. These data underscore the need for prolonged combined antiplatelet treatment among patients treated with DES, a fact that increases the total cost of the procedure and affects the cost-effectiveness analysis of these devices. Despite being a relatively rare phenomenon, late stent thrombosis is catastrophic since it leads to acute myocardial infarction or death, with the obvious medical as well as legal consequences;[46] thus, it is important for physicians to recognise the risk of late stent thrombosis.

Several cost analyses have been performed to assess the economic burden of restenosis to the health care system. Cost-effectiveness analysis is a method for comparing the expected benefits of a medical technology with the net cost of this technology. This relationship is expressed by an index called "incremental cost-effectiveness ratio" (ICER) and for PCI results it represents the cost of avoiding an additional, clinically driven, target vessel revascularisation during follow up. This index is calculated by the formula (Cost of DES – Cost of BMS / outcome of DES – outcome of BMS). Cost-effectiveness analysis studies provide a useful framework that can be used to support the development of DES treatment guidelines. They take into account the frequency of clinically important restenosis and the additional health care costs associated with its treatment, which vary according to the population characteristics of the specific patients under investigation and to the features of the healthcare system where they are applied.

In 2004, Cohen et al presented a cost-effectiveness analysis of the SIRIUS trial, among patients with complex coronary stenoses who were treated with CYPHER™ stents or conventional BMS. Initial hospital costs were increased by $2881 per patient with SES. During the one-year follow-up period, use of SES led to significant reduction in the need for repeat revascularisation procedures and to a decrease in the follow-up costs by $2571 compared to BMS. The net increase of one-year cost was estimated at $309 per patient treated with SES.[47] The authors concluded that the use of SES in patients with complex coronary stenoses appears to be reasonably cost-effective, and with the availability of new, longer stents it would reduce total one-year costs compared with BMS, even being cost saving.

In an analysis of the RAVEL trial, van Hout et al showed that DES use was associated with an increase of initial hospital cost by €1286 per patient.[48] However, because of the fewer revascularisation procedures during one-year follow-up (11.1% fewer MACE) among patients treated with DES, the final additional one-year cost was estimated at €166. The authors concluded that there is an attractive balance between costs and effects of SES in the treatment of single and simple native *de novo* coronary lesions, while the cost-effectiveness of DES in complex lesions remains to be determined. Nevertheless, it has to be emphasised that in this trial the cost of purchase for both SES and BMS used was much cheaper than in other trials.

Greenberg et al, using a logistic model of PCI cost-effectiveness analysis among patients with single vessel CAD, showed that treatment with DES could be cost-effective for patients with estimated re-intervention likelihood with BMS greater than 12%, and even cost saving for patients with estimated re-intervention likelihood greater than 20%, especially if the therapeutic alternative for these patients is invasive and expensive surgery.[39]

According to this model, and with the current prices of the devices, DES implantation seems to be cost-effective for the great majority of diabetic patients, except probably these with short, discrete lesions in large vessels (≈4.0 mm diameter). For non-diabetic patients DES implantation is cost-effective in the treatment of lesions in small vessels (<3.0 mm) and long lesions in relatively large vessels (≤3.5 mm).

Serruys et al, in a cost-effectiveness analysis of the RESEARCH and T-SEARCH registries, showed a non-satisfying ICER of €29373 for SES in order to avoid an additional clinically driven target lesion revascularisation procedure in real world PCI cases and €22960 for PES in a similar cohort of patients.[49] He estimated the cost-effective price of DES to be around €1200-1500, instead of the current price of €2500-3000, and proposed a price for these devices around €1000

in the future, as the price of the comparators BMS tend to fall, in order to achieve a high cost-effectiveness ratio and widespread use of DES in the majority of CAD patients.

Finally, a recent cost-effectiveness analysis of the BASKET trial, comparing DES with third-generation cobalt alloy BMS in a real world setting, showed that unrestricted DES implantation in multi-vessel patients treated with PCI led to a 44% overall post-procedure reduction in the rate of major events compared to BMS, probably because of the greater efficacy of these BMS compared to the old stainless steel ones.[50] The ICER of DES to avoid a major event was €18311 (€19264 for CYPHER stent and €16694 for TAXUS stent), substantially higher than the widely acceptable limit of €10000 per event avoided. The investigators concluded that the use of DES could be restricted to certain high-risk patient subgroups, such as diabetics and elderly patients with three-vessel disease, long and/or multiple treated segments in small vessels, where DES use seems to be cost-effective or even cost-saving, at least until the prices of these devices are reduced.

Two recently published papers also contribute to the DES cost-effectiveness issue. Rinfret et al[51] analysed the data of CYPHER stent implantation among moderate to high restenosis risk patients of the C-SIRIUS trial in Canada. They reported that, with an average ratio of 1.5 stents per lesion implanted at a price of $2700 per SES, compared with $700 for BMS, the ICER of SES versus BMS was $11275 per repeat revascularisation avoided at one year—borderline cost-effective in relation to the acceptable limit of €10000 per event avoided. They emphasise that with a lower ratio (1.2) of stents per lesion using longer stents, unavailable during the study, ICER would be improved to $7941 and concluded that SES implantation increases initial net healthcare costs but seems to be cost-effective for high risk patients undergoing single-vessel revascularisation.

Bakhai et al[52] performed a prospective economic evaluation of patients included in the TAXUS-IV trial, undergoing PCI with PES or BMS. They reported that with an average ratio of 1.3 stents per lesion, implanted at a price of $2700 per PES compared with $800 for BMS, the ICER of PES versus BMS was only $4678 per target vessel revascularisation avoided, and in 86% of the total patient population ICER remained below the acceptable limit of $10000. The authors concluded that, despite the initial increase of PCI cost compared to conventional BMS implantation, the use of PES is associated with reduced follow-up health care costs, leading to an ICER per target vessel revascularisation event avoided comparable to several other well accepted devices for the reduction of coronary restenosis, such as BMS or vascular brachytherapy. Implantation of PES seems to be cost-effective for high risk patients, such as diabetics and patients with lesions in small diameter vessels, but unattractive, for the moment, for patients with reference diameter vessels >3.0 mm.

In summary, DES use during PCI substantially reduces restenosis of the treated lesions and repeat revascularisation procedures, resulting in a high demand for these devices from both physicians and patients and an initial increase in health care costs. Patient selection for DES implantation is an evolving issue that should be based on careful assessment of therapeutic benefit, adverse events, need for prolonged antiplatelet treatment, implementation in various subgroups and indications, as well as cost-effectiveness results. The cost-effectiveness of DES depends on the target population features and the specific treatment comparator (BMS, CABG or medical therapy). According to the data of available economic analyses and clinical trials, DES, given their current price, will be reasonably cost-effective for a great percentage of patients and even cost saving for the subgroup of patients who are at the higher risk of clinical restenosis with the conventional PCI techniques.

It has to be mentioned that, in the past, worthwhile techniques such as balloon angioplasty were introduced with a procedural cost of $4300 and coronary stenting was performed at a cost of $4400. The main impediment to the wider application of DES in daily interventional practice and to the higher penetration rate of these devices in the non-surgical treatment of CAD is, up to the moment, their high price. In the future, anticipated lower costs of DES should render this technology cost saving for a larger group of PCI patients, broadening the target population, even for the treatment of vulnerable plaques, which are the next hot spot of interventional cardiology.

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