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Cost Effectiveness of Drug Eluting Stents

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ABSTRACT

Drug eluting stents (DES) have ushered in a new era in non-surgical coronary revascularization with substantially reduced rates of restenosis, albeit at an increased expense for our health care system incurred by their higher cost compared to bare metal stents (BMS) and by a high demand of these devices by both physicians and patients. The risk of late thrombosis and other safety issues will need to be further investigated. The cost-effectiveness of DES depends on the features of the target population, the higher DES cost, any remaining safety issues and the specific treatment comparator (BMS, surgical or medical therapy). According to the data of economic analyses and clinical trials, DES will be reasonably cost-effective for a great percentage of patients and even cost saving for the subgroup of patients who are at high risk of clinical restenosis with the conventional PCI techniques. The main limitation of wider application of DES in the daily interventional practice remains their high price, which if lowered in the future will broaden their target population in interventional cardiology.

Drug eluting stents (DES) represent one of the most innovative developments in interventional cardiology and the third (post balloon PTCA and metallic stent development) blasting innovation, which determined a dramatic change in the treatment practice of coronary artery disease. It is widely known that the main drawback of non surgical treatment (percutaneous coronary intervention-PCI) of coronary artery disease patients with either balloon angioplasty or stent implantation is the restenosis of the treated lesions, that leads to recurrence of symptoms and worsening of quality of life. Restenosis is a typical healing process to the vessel trauma produced during the transluminal procedure of angioplasty and consists of elastic recoil of the dilated artery and neo-intimal proliferation, which is a biological response to the mechanical injury. The rate of post-PCI restenosis varies from less than 5% to over 50% depending on the different clinical and anatomical features of patients treated.

Drug eluting stents associate an anti-proliferative 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. Up to date extensive investigation of DES in clinical practice includes the sirolimus-eluting stents (SES CYPHER™) and the paclitaxel-eluting stents (PES TAXUS™). Implantation of these devices, compared with bare metal stents (BMS), has led to a dramatic decrease of post PCI restenosis rate in the first pivotal clinical trials as well as the large randomized studies performed throughout the world [1-6], indicating that the risk of restenosis can be reduced by 49% to 81% when drug-eluting stents are used to treat new and relatively non-complex lesions included in these trials. In every day "real world" practice also, compared with an

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historical control trial ARTS [7], DES effectiveness over BMS has been definitely documented according to RESEARCH registry data [8]. More recently data from the T-SEARCH registry [9] and the ARTS II study [10] which included patient subsets with more complex and higher restenosis-risk lesions, confirmed the improved results of DES over BMS and showed for the first time non inferiority of DES PCI to coronary artery bypass grafting (CABG) surgery in the treatment of patients with multivessel coronary artery disease. As a result, from the clinical point of view, introduction of effective DES allowed physicians to treat patients with more complex and high restenosis-risk lesions, such as diabetics or patients with long lesions in relatively small vessels, proximal location and total occlusions, who were treated before with CABG. This circumstance translated into a great increase in the quality of life of these patients.

COST OF DES

However, although clinical benefits of DES usage are increasingly evident, important concerns about their cost have been raised in the medical community. The increased cost of a DES is the final result of higher research and development costs of the manufacturing companies, the expenditure of acquisition of exclusive and valuable licenses from pharmaceutical companies, the need of new manufacturing facilities for new designs and the relative low production levels [11]. Generally, the price of a DES is at least three-fold higher than the price of a conventional BMS and most authors report implantation of 1.5 stents per patient treated, leading to a significant increase of the initial total cost of the procedure. According to data from Lemos et al [11], the unrestricted use of DES in all USA patients that currently receive standard BMS would cost the health system about \$1.5 billion each year. Moreover, Greenberg et al [12] estimated that uniform conversion of all current standard BMS procedures to DES would result in an initial cost increase of about \$2800 per patient treated. Consequently, the great economical impact on healthcare budget, which is associated with the extensive use of DES remains a crucial issue, affecting worldwide socioeconomic policy.

COST-EFFECTIVE ISSUES

Issues concerning cost-effectiveness of DES include questions about the impact of DES implantation on “hard clinical” end-points such as death or reinfarction, and about the reduction of post-PCI restenosis rate in real world practice and special patient subsets. Further questions relate to the impact of DES on need for CABG either as a primary procedure or during the post-PCI follow up period, the long term effective-

ness of DES in treating coronary artery disease patients and both short- and long-term safety of these devices.

EFFECT ON MORTALITY

The main concern arises from the fact that DES use does not affect mortality post PCI procedures. All the available data show no influence of DES implantation on mortality rate following the procedure, when compared to the BMS. Indeed, the 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). Similar pooled analysis of 4 clinical trials (SIRIUS, E SIRIUS, C SIRIUS and RAVEL) using CYPHER™ stents in 1748 patients showed again 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 randomized trials, Babapulle et al showed that DES use had no impact on mortality or myocardial infarction (MI) rate in comparison to BMS [6]. On the other hand, the main effect of DES implantation, that is the reduction of restenosis rate, is a secondary outcome and up to date no study has demonstrated a definite link between restenosis and mortality [13], except one report of BMS use mostly in diabetic patients [14]. Consequently, despite the clear clinical benefits, concerns remain on whether the additional costs associated with the reduction or even elimination of restenosis are worth paying.

RISK OF RESTENOSIS

It is widely acceptable that restenosis cannot be predicted. Multivessel stenting and diabetes are the two main patient related variables increasing the possibility of restenosis. Lesion related variables correlated with restenosis risk are the size of the vessel, the lesion length and consequently the stent length, the minimum lumen diameter pre- and post-procedure, the location or the type of lesion (ostial, occlusion, bifurcation) and the presence of multiple stents. So, it is anticipated that in diabetic patients with high grade long lesions in multiple small size (<3.0 mm) vessels, restenosis risk is the highest.

Post-PCI restenosis rate is derived mainly from the results of randomized clinical trials. It is well established that DES usage in patients with simple and low restenosis-risk lesions leads to an exceptionally significant decrease of restenosis rate when compared to BMS [1,2,4,15-17]. When used in patients with more complex lesions or special conditions the results still remain far better but nevertheless not so favourable as in simple lesions [3,5,18-20]. The increased, compared to BMS, efficacy of DES in the treatment of daily practice patients

with high risk and complex lesions has been confirmed by the recent big registries' results [8-10], while the comparative efficacy of these devices to CABG will be shown when the results of the on-going mega trials FREEDOM and SYNTAX are presented.

Long term efficacy of SES in preventing restenosis of the dilated lesions has been established by several studies [21,22]. Recently, the 2-year follow-up data of RESEARCH showed persistent lower rate of clinically driven target vessel revascularization (TVR) among patients treated with SES in comparison with BMS (6.4% vs 14.7% respectively) [23]. The long-term follow-up also of the TAXUS trials showed persistently increased efficacy of PES in preventing new target lesion revascularization (TLR) procedures and total major adverse cardiac events (MACE) rate.

According to ARTS II study data, patients treated with DES PCI present during a follow-up of 1 year similar course with that of patients treated surgically in the ARTS study. Patients of ARTS II showed 1.0% mortality rate, 1.2% new MI rate, 7.4% re-intervention rate and total MACE rate of 10.4%. On the other hand, patients of the ARTS study treated surgically presented a mortality rate of 2.7%, 3.5% new MI rate, 3.7% re-intervention rate and total MACE rate of 11.6%. These data underscore the non inferiority of DES PCI to CABG, with a clinical implication of leading many patients and physicians to select PCI with DES implantation as the primary treatment option of coronary artery disease instead of CABG. Moreover, the decreased need for re-interventions, due to lower rates of restenosis and TLR among patients treated with DES implantation, leads definitely to a lower need of CABG post DES PCI compared to BMS PCI.

Stent thrombosis and other safety issues. Finally, as far as the safety of these devices, all the available data show no difference in subacute or late thrombosis rate between DES and standard BMS, if proper antiplatelet therapy is given. The reported low rate of very late thrombosis, associated especially with PES, is a unique finding necessitating long-term combined antiplatelet therapy at least in some special cases [24]. The finding of increased rate of late stent malapposition among patients treated with DES in some studies has not been correlated with an adverse event and so it cannot be counted as a safety issue. The only unsolved safety issue is the "late catch-up" phenomenon described by Virmani et al [25], that represents an inexplicable increase of restenosis rate between 6 and 12 months or even later with some special type of DES. From all the above mentioned, it is clear that DES are effective and safe devices in reducing (compared to BMS) restenosis and the need for a new revascularization procedure rate in about 75% of patients with coronary artery disease treated non surgically, without affecting mortality. Their use is correlated with higher procedural and initial cost of PCI comparing to BMS.

Analyses of cost-effectiveness. Several cost-effectiveness

analyses have been performed to access the economic burden of restenosis to the health care system. 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 specific patients' population characteristics under investigation and to the healthcare system reality where they are applied. Cohen et al [26] presented in 2004 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 1-year follow-up period, use of SES led to significant reduction in the need for repeat revascularization procedures and of the follow-up costs by \$2571 compared to BMS. The net increase of 1-year cost was estimated at \$309 per patient treated with SES. 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 1-year costs compared with BMS.

In another analysis of RAVEL trial, among patients with rather simple and low restenosis-risk lesions who were treated with either CYPHER™ stents or BMS, van Hout et al [27] showed that DES use was associated with an increase of initial hospital cost by €1286 per patient. However, due to less revascularization procedures during 1-year follow-up (11.1% less major adverse cardiac events-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 cost effectiveness of DES in complex lesions remains to be determined. Nevertheless, it has to be emphasized that in this trial the cost of purchase of both SES and BMS used was much cheaper than the other trials.

Greenberg et al [12] showed that treatment with DES could be cost-effective for patients with estimated re-intervention likelihood 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 the invasive and expensive surgery. Finally, Serruys [28] in the cost-effectiveness analysis of RESEARCH and T-SEARCH registries estimated the cost-effective price of DES to be around €1200-1500, instead of the current price of €2500-3300.

CONCLUSION

In summary, DES use during PCI substantially reduces restenosis of the treated lesions and repeat revascularization procedures, resulting in a high demand of these devices by both physicians and patients and in an increase of health care costs. 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 economic analyses and clinical trials, DES will be reasonably cost-effective for a great percentage of patients and even cost saving for the subgroup of patients who are at high risk of clinical restenosis with the conventional PCI techniques. It has to be mentioned that in the past worthy techniques such as balloon angioplasty was introduced with a procedural cost of \$4300 and coronary stenting was performed at a cost of \$4400 [11]. The main limitation of wider application of DES in the daily interventional practice and higher penetration rate of these devices in non surgical treatment of coronary artery disease is, for the moment, their high price. In the future, 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 is the next hot spot of interventional cardiology.

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