All Patients Undergoing PCI Should Receive Drug Eluting Stents

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ABSTRACT

Coronary stent implantation is the main therapeutic approach to coronary stenosis in interventional cardiology. Attention is now focusing on the concept of local pharmacologic intervention by drug eluting stent. Though, the newer molecules - Sirolimus and Paclitaxel have been shown to be effective in de-novo lesion with remarkablely low restenosis rate, these finding has also provoked profound skeptism. The major criticism focused on the lack of data in *complex lesions* and on the lack of *long-term* data. Also Drug Eluting Stent (DES) has failed to achieve the expectant results and requires further refinement to improve the percutaneous approach in most patients with multivessel coronary disease. The cost effectiveness depends on the target population the specific treatment comparator (bare metal stent, CABG or medical therapy), as well as on the perspective of the analysis. In the future lower incremental cost for DES might render this technology cost saving for a much larger subgroup of percutaneous coronary intervention (PCI) patients and broaden the ideal target population.

INTRODUCTION

Intracoronary stenting is a major advance in treatment of coronary artery occlusive disease since the advent of PTCA in 1977.[1] Stents were introduced in 1989 for emergency treatment for acute complications of PTCA. Later on, elective stent placement began in 1994 with two randomized trials showing reduced rates of restenosis.[2,3] The number of percutaneous interventions with stenting, performed each year has expanded considerably, since the early years. However many of these patients develop exaggerated vascular neointimal proliferation after stenting, leading to in-stent restenosis (ISR). Later DES emerged to prevent ISR. After the FDA approval of DES for clinical use, a total of 4, 50,000 Cypher stents (Cordis Corp) have been used worldwide as of October 20, 2003 reflecting an increasing percentage of patients treated with coronary stents.[4]

CONCERNS AND SCIENTIFIC EVIDENCES

The clinical evidence for superiority of DES against bare metal stents came from two initial studies- the first-in-man (FIM) study[5] and the RAVEL study[6] (RAndomized study with the sirolimus eluting Bx Velocity balloon expandable stent in the treatment of patients with de novo native coronary artery lesion). Both these studies included patients with single non-complex de novo lesions and the rate of binary angiographic restenosis (diameter stenosis > 50%) was zero at 2 years and 6 months respectively. However the results of these studies cannot be extrapolated to the wide variety of patient undergoing "real world" angioplasty. Later on the pivotal SIRIUS trial[7] included only patients with single lesion in one vessel between 2.5 and 3.5 mm in diameter and from 5-30 mm in length. However in this study, patients with acute myocardial infarction, severe unstable angina or chronic renal failure were excluded. Lesions in saphenous vein grafts, bifurcation lesions, total occlusions and in-stent restenotic lesions were also excluded from the study. *Restenosis did occur in 9% of all the cases and in diabetic patients, in- segment restenosis was observed in 23.7 % of cases*. Pooled data from various clinical trials [8] of Sirolimus eluting stents shows restenosis after Cypher stent in up to 9% of all patients, 18% of all diabetics (35% of insulin dependent diabetics) and 16 % of patients with small-caliber target vessels. These facts clearly demonstrate that DES is not restenosis-proof.

In view of insignificant presentation of patients with multivessel coronary disease in previous studies, D Orlic et al[17] evaluated the safety and efficacy of Sirolimus Eluting Stent (SES) in this group. At a mean follow-up of 6.5 months in their study, the 22.3% MACE rate was mainly driven by a need for 16 % revascularization; and the increase in need for revascularization per patient occurred due to treatment of multiple lesions. Authors concluded that persistent of new revascularization procedures suggests that need for a better understanding of the reasons for the failure of percutaneous approach in most patients with multivessel coronary disease.

There are other limitations also in the evidence-based support for DES. Only the E-SIRIUS Trial[9] has tested direct stenting with DES to date. None of the available trials have permitted the use of athero-ablative technologies before DES deployment. Hence,

DES is currently contraindicated in patients who are judged to have a lesion, which prevents complete inflation of an angioplasty balloon.[10] Cumulative dose of sirolimus has been a concern when more than two DES are used in a patient. The potential adverse effect of this is unknown. However, increased drug delivery along with co- administration of drugs that may increase sirolimus blood concentration like calcium channel blocker, antifungal, macrolide antibiotics, cimetidine, danazol etc., may have adverse effect over the vascular endothelium.[10] There are no data showing safety of use of more than two stents till date and increased sirolimus antagonizes the conversion of clopidogrel to its active moiety and thus diminishes the platelet inhibitory effects of clopidogrel.[10]

Brachytherapy is the only successful treatment for in-stent restenosis available to date.[11] However, brachytherapy for restenosis in DES is not well studied. There are concerns about the degradation of polymer coat in the stent.[10] In short, the relative safety and efficacy of DES in high risk complex lesions like, thrombus containing lesions, ostial or bifurcation lesions, saphenous vein graft lesions, unprotected left main lesions, chronic total occlusions, vessels < 2.5 or >3.5 mm in diameter or diffuse in-stent restenosis, have not been established. In real world, the total numbers of patients with these types of complex lesion are seen in significant proportion and treating these patients with DES may not be justified with the current evidence of support.

POTENTIAL COMPLICATIONS

In a few cases reported by Virmani R et al[12] and others, late thrombosis 18 months after receiving drug eluting stents for unstable angina have been described. The histological study revealed aneurysmal dilatation of stented arterial segments with a severe localized hypersensitivity reaction with predominantly T lymphocytes & eosinophils. Luminal surface of the stent showed fibrin-rich thrombus with sparse smooth muscle cells. The authors proposed the hypersensitivity to the polymer coat, as etiology rather than metallic stent or sirolimus. Another similar report from Liistro et al[13] described the "late catch up phenomenon" (loss of initial anti-proliferative effects) following high dose paclitaxel derivative-QP2 eluting stent and potential aneurysm formation. In fact, certain DES have already been proven to be ineffective in reducing restenosis with even worse results being reported, as compared with conventional bare metal stents.[14] In the RAVEL trial,[5] the late stent strut malapposition (IVUS proved) at 6 month was more common in DES patients than in the control arm.

Two recent FDA public notifications[15] have warned physicians of two potential adverse effects of DES-hypersensitivity reaction and sub acute thrombosis. Up till October 20, 2003, more than 290 occurrences of sub acute stent thrombosis have been reported and more than 60 patients have died. Even though this rate is comparable to the rate with bare metal stents, the real incidence may be even higher as there is no uniform registry to report the events following DES implantation.

COST FACTORS

The high cost of DES is attributed to the developmental & research costs, acquisition of licenses from companies, need for new manufacturing facilities etc. In the Western world, the main concerns are about the redistribution of budgets and priorities in the health system, with a shift of huge amount of money to the manufacturers, when there is a substantial movement from CABG to DES. The scenario in India is different. In a country where only a small percentage of patients enjoy health insurance policies, not too many can really afford the cost of DES. Therefore, certainly one should not propagate the practice of prescribing DES in multivessel disease and /or complex coronary lesions in absence of definite data from clinical studies and cost benefit analysis.

WHERE ARE WE?

Even though DES has reduced restenosis rates in selected cases, the utilization is still limited because of the cost constraints and lack off reimbursement universally. The initial euphoria stimulated by the RAVEL study has not been sustained in subsequent studies with slightly more complex lesions. In a recent article by William O'Neill[16] he recommended guidelines for use of DES, in the format of ACC/AHA Task force on practice guidelines. In this class I indications are obtained from inclusion criteria of the three randomized clinical trials (SIRIUS, RAVEL, and TAXUS II). Class II and III are derived from subgroup analysis of these trials and from soon-to-be published registries. Evidence level A is derived from multiple randomized trials, and level B is from single randomized trials or registries. It should be emphasized that only relatively small number of diabetic patients and even fewer insulin treated diabetics have been studied. The guidelines are as follows.

Class	Condition (Level of evidence)
Class I	1. Lesions 15-30 mm in length & 2.5-3.5 mm in diameter with 50-99% obstruction pre procedure (A)
	2. Diabetes (B)
	3. Lesions < 15 mm in length & 2.5-3.5 mm in diameter (B)
Class II a	1. Ostial RCA, LAD, LCX or protected left main lesions
	2. Parent vessel bifurcation lesions with PTCA of side branch.
Class II b	1. Recanalized CTO
	2. Lesions > 30 mm in length and 2.5-3.5 mm in diameter.
	3. In-stent restenosis- focal pattern.
Class III	1. SVBG lesions.
	2. In-stent restenosis- diffuse pattern.
	3. Unprotected left main lesions.

SUMMARY

This, in fact, is a guideline in evolution and requires periodic revisions based on results of ongoing clinical trials and registries. The new technology of DES came into medical practice with promise to revolutionize the field of interventional cardiology. However DES is a technology in evolution and cannot be applied to all patients undergoing percutaneous coronary interventions. Well-designed, rigorous and large studies are required to address

the potential gaps in safety and efficacy. The clinicians should carefully verify the evidence from the trials and judiciously apply the results for the best benefit of the patients.

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