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The Choice Of Optimal Coronary Stents: Is It Possible To Maximize Cost-Effectiveness?

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Abstract

Percutaneous coronary interventions (PCI) with implantation of the stent have become standard-of-care in the management of obstructive coronary artery disease (CAD), including amongst patients with acute coronary syndromes (ACS). The most expensive hardware in PCI is drug-eluting stent (DES), thus making PCI an expensive affair; leading to unaffordability in many parts of the world. We made an attempt, to identify improved cost-effective ways to substitute DES with bare-metal stent (BMS) as and when feasible, while preserving the interests of the patients. While for patients with unstable CAD, DES is superior to BMS in device-oriented outcomes (unlike in patient-oriented outcomes); patients with stable CAD with lesion (type A/B1 morphology) with coronary vessels larger than or equal to 3.75 mm: BMS is as good as second-generation DES, in both patient-oriented composite outcomes (all-cause death, any myocardial infarction, MI; and revascularization) and in device-oriented composite outcomes (cardiac death, target vessel MI, or symptom-driven TLR) both in short- and long-term follow-up. For patients with very-high risk of bleeding, irrespective of the cause of bleeding: BMS may be preferred with a view to reducing bleeding complication (as major bleeding adversely affects prognosis). Prefer no stent strategy i.e., only plain old balloon angioplasty (POBA) as and when possible like for patients with focal tandem stenotic-aneurysmal lesions and in diabetic patients with acute coronary syndromes with triple-vessel disease (planned for coronary artery bypass, POBA to relieve the obstruction to achieveing TIMI 3 flow, if possible). Replace temptation of oculostenotic reflex with the objective assessment of ischemia with flow fractional reserve (FFR) for lesions between 50% and 90%, particularly in stable CAD. Of course, for patients with obstructive left main stem (LMCA) disease and for bifurcation lesions (needing 2 or more stent strategy), and for lesions with Type B_2 / C morphology, use of DES (preferably second-generation) to improve both patient-oriented and device-oriented outcomes is cost-effective and is recommended.

Keywords: Bare-Metal Stent (BMS); Drug-Eluting Stent (DES); Coronary restenosis; Coronary artery size; Coronary stent size; Patient-oriented outcomes; and device-oriented outcomes in Percutaneous Coronary Interventions (PCI); Choice of stent the most cost-effective stent;

Introduction

Percutaneous Coronary Interventions (PCI) has become standard-of-care management of obstructive Coronary Artery Disease (CAD), Particularly in Acute Coronary Syndromes (ACS). Only balloon dilation i.e., plain old balloon angioplasty (POBA) despite reducing coronary stenosis and improving symptoms, had unacceptable restenosis rates and at times catastrophic abrupt vessel closure. A bare-metal Stent (BMS) was invented to overcome such issues. The improved results with BMS were sensational as it reduced catastrophic abrupt vessel closure and restenosis significantly [1]. However with increasing experience, the enthusiasm with BMS gradually faded, as more and more patients with restenosis (though less than that with POBA) were encountered. As neointimal proliferation was the main culprit for stent restenosis, cytotoxic drugs (paclitaxel and sirolimus)-eluting stents were developed in an attempt to further reduce restenosis rates. However, all the technology-related innovations had their limitations, like the need for longer duration of dual antiplatelet drugs for 1-year and greater cost thus leading to unaffordability in most countries. With the epidemic of CAD particularly in developing world coupled with the higher cost of DES (3 to 5 folds higher than BMS), many health insurance-systems or government-sponsored health-care systems became overstretched. There is impending need to address this issue, if we wish to preserve and further the art and science of coronary stenting.

The weakest link in wider implementation of any new technology, (no matter how good and useful): is cost-effectiveness. In an attempt to choose the best cost-effective strategy many trials were conducted, however most had the follow-up until three years. In 2005, the cost-effectiveness analysis of BASKET trial [2] and the other trial in 2006 [3] showed the use of first-generation DES in real-world practice with selected patients is less cost-effective as compared with cobalt-chromium BMS. In another cost-effectiveness analysis DES is shown to be cost-effective only when BMS restenosis exceeds 18.5% [4].

The Mechanism of Post-Stenting Restenosis

The implantation of stent carries the definite amount of injury to the vessel wall at the site of balloon inflation and stent implantation. The vessel expansion is due to compression of the soft atheromatous material, stretching the vessel wall and finally

disrupting the intima and varying degree of intimal dissection [1]. These processes initiate neointimal proliferation and hyperplasia. The neointimal process involves differentiation of smooth muscle cells associated with macrophage accumulation and extensive neovascularization [5]. This leads to restenosis. In order to overcome restenosis, DES was developed. DES releases anti-inflammatory, immunomodulatory, and antiproliferative agents like paclitaxel or sirolimus over 30 days minimizing neointimal proliferation to reduce restenosis, albeit at slightly increased risk of life-threatening stent thrombosis. The second-generation DES was invented, primarily to reduce stent thrombosis (early, late and very-late) seen with first-generation DES. The second-generation DES comprises thinner struts, increased biocompatibility, and reduced thickness of durable or biodegradable polymers, with different limus (everolimus or zotarolimus) than do first-generation drug-eluting stents. These properties translate into reduced stent thrombogenicity in experimental models and clinically with improved stent thrombosis (around 0.5% per annum) [6,7].

Previous studies with BMS demonstrated a similar late lumen loss irrespective of vessel sizes.[8] As per estimates, the mean late luminal loss is around 0.17 mm in DES, as compared with 0.8 mm to 1.00 mm with BMS.[9,10] This means for the same extent of late lumen loss which could easily be accommodated in larger vessels, in smaller vessels this may cause hemodynamically-significant narrowing of the coronary vessel. Studies have shown low restenosis rate (<10%, closer to that observed with DES) in larger coronary arteries with BMS [8, 11, 12].

The Impact of Vessel Size on the Type of Stent

In a study comparing 1-year event-free survival with different vessel sizes (<2.8mm, 69.5%; 2.8-3.2mm, 77.5%; and >3.2mm, 81%; p<0.001), the restenosis rate of small vessels was 1.5 fold or higher than that observed with in larger vessels [8]. In another comparison study between DES and BMS at vessel diameter <3mm. DES had significantly lower Major Adverse Cardiac Events (MACE) and Target Vessel Revascularization (TVR) than BMS in 645 patients up to 3-year follow-up [13]. Not only randomized trials showed benefit with DES. The real-world data also supported the same conclusion [14], including amongst elderly (> 75 years), albeit without any difference in total mortality, MI, stent thrombosis or bleeding [15].

The second-generation DES in various studies conducted in small vessels continued to show superiority in terms of MACE and TVR/ Target Lesion Revascularization (TLR) as compared with BMS [16], and on comparing EES with PES [17]. However such beneficial results were not seen with Bioresorbable Vascular Scaffolds (BVS) in small vessel lesions [18, 19].

Notably, the results of using stents in larger vessels are different. A database analysis of 466 patients (using BMS and first-generation DES) in 2007 showed no difference in outcomes, including TLR in patients with coronaries = or > 3.5mm (even after adjusting stent diameter, stent length, and the presence of diabetes mellitus). Moreover, there was no difference in stent thrombosis [20, 14]. The superiority of DES diminished with increasing diameter of the vessel along with decreasing length and complexity of lesions. With coronary diameter > 3.5mm, BMS is as effective as DES (particularly second-generation) in preventing recurrent Myocardial Infarction (MI) or death albeit with increased rate of angiographic binary stenosis, particularly in setting of acute coronary syndromes [21-24]. At cut-off point diameter of 3.75 mm almost all benefits of DES, like death, recurrent MI and/including TVR equalize with that of BMS [25, 26].

The story in ACS is rather different. In view of highly thrombogenic milieu the stent thrombosis rates and restenosis rates are higher. Thus studies suggest implantation of BMS in vessels with a diameter of 3.5 mm or more is still associated with a higher risk of restenosis in ACS patients [27, 28]. The stent thrombosis with DES particularly in the smaller vessel is another issue worth consideration. In a multicentre Asian registry Nakamura et al. showed incidence of stent thrombosis to be relatively low (0.5% with DES and 0.6% with BMS of subacute stent thrombosis), and 7-year analysis disclosed higher late stent thrombosis in DES than in BMS (0.185 vs. 0.1% respectively, p=0.001) [29]. However other studies with smaller vessels did not show the difference between DES and BMS in stent thrombosis in smaller vessels [30]. It appears in these studies and in most other studies, stent thrombosis rates are quite low (0.50 to 1% per year) making the true comparison of stent thrombosis non-conclusive.

Apart from vessel size and the setting of ACS, many variables are known to affect restenosis rates. Clinical variables (diabetes mellitus, chronic renal failure, cardiac allograft vasculopathy following orthotropic cardiac transplantation), Lesion morphology (chronic total occlusion, CTO; long lesions, saphenous venous graft disease, bifurcation lesions, and lesions with Type B_2 and type C morphology, vulnerability of the plaque, poor distal run-off etc.), procedural characteristics (final minimal lumen diameter, geographic miss, and re-stenting, suboptimal preparation of the lesion bed before stenting, suboptimal expansion and alignment of the stent struts with the vessel wall, landing the distal edge of the stent at the lipid-rich core of the plaque etc.), operator-related factors (the experience of the operator, availability or judicious use of the facilities like intravascular ultrasound, IVUS; optical coherence tomography, OCT etc.), and institution-related factors (heavy-volume versus low-volume centers, team work versus solo operators etc.). These variables are well-known/well-documented [31]; therefore they are outside the scope of the present article.

In patients following coronary artery bypass surgery (CABG), treatment of saphenous vein graft disease with PCI even without affecting long-term outcomes MACE (MI, mortality, cardiac death, and stent thrombosis), DES significantly reduced the risk of TLR, target vessel failure (TVF), and TVR as compared with BMS in short-term [32].

Importantly, no study including 6-years long-term results of Norwegian NORSTENT trial [33] (except recent 5-years results of EXAMINATION trial [34], which are considered as hypothesis-generating) has shown the reduction in total mortality with DES so far.

The definite superiority of the third-generation stents (with biodegradable polymers, polymer-free and biodegradable stents on the basis of poly-L-lactide or magnesium) is under close scrutiny; at present hard to comment till long-term results of randomized trials and real-world data from various registries are published in peer reviewed journals.

Conclusion: choice of the most cost-effective stent?

Although DES remains the default device for implantation in most cardiac catheterization laboratories around the globe. However in the resource-limited settings (invariable in developing countries) most health-care are the self-finance affair. In the developed world, health-insurance systems are overstretched and health policy premiums are getting increasingly out-of-pocket of a common man. Most government-funded healthcare systems even in the developed world are slowly failing. No advancement in technology (no matter how good it is) can thrive unless cost-effective. Therefore cost-effectiveness assumes paramount importance. Now we have sufficient experience and data to draw some cost-effective and pragmatic conclusions:

1. For patients with stable CAD: with vessels larger than or equal to 3.75 mm, and the lesions with type A and B_1 morphology. BMS is as good as second-generation DES, in both patient-oriented composite outcomes (all-cause death, any myocardial infarction, MI; and revascularization) and in device-oriented composite outcomes (cardiac death, target vessel MI, or symptom-driven TLR) both in short- and long-term follow-up.

2. For patients with unstable CAD: irrespective of vessel size, prefer DES despite being not superior in patient-oriented composite (all death, all MI, or any revascularization) but superior in device-oriented composite outcomes (cardiac death, target vessel MI, or symptom-driven TLR).

3. For patients with lesions in the left main coronary artery (LMCA), bifurcational lesions (needing 2 or more stent strategy), and for lesions with Type $B_{2/}$C morphology, use DES (preferably second-generation) to reduce patient-oriented and device-oriented outcomes.

4. For patients with the potential of needing elective/semi-urgent surgery (except low-risk of bleeding during surgery) within 3 months in stable CAD and within 6 months to 1 year in unstable CAD, particularly with type A/B_1 lesions in vessel >3 mm: BMS is perhaps a safer alternative.

5. For patients with atrial fibrillation (in need of warfarin/novel oral anticoagulants) or patients with compliance issues with dual antiplatelets or patients with very high-risk of bleeding and in need of stenting: prefer BMS, as a safer choice to limit the duration of dual antiplatelet regimen to 1 month to reduce the risk of bleeding.

6. For patients with saphenous venous graft disease: DES may be preferred particularly in view of reduced short-term MACE, TVR and TLR.

7. Prefer no-stent strategy: 1) In dilation of the distal anastomotic stenosis of left internal mammary artery with left anterior descending artery (LAD), 2) Very focal tandem stenotic-aneurysmal lesions (to relieve stenosis, stent is best avoided to prevent stent thrombosis in the adjacent aneurysmal segment), 3) Particularly amongst diabetic patients with ACS with triple-vessel disease (planned for coronary artery bypass, POBA to relieve the obstruction to achieve TIMI 3 flow, if possible) 4) Patients with largely thrombotic lesions (with minimal plaque burden or with plaque erosion) in ACS, 5) Patients with poor flow in the distal coronary artery, particularly in the setting of ACS, and 6) Amongst patients with smaller coronaries (< 2.25 mm in diameter).

8. For patients with stable CAD: for lesions between 50% and 90% stenosis, always resist oculostenotic reflex (a common occurrence), prefer to assess/document functional significance of lesion with flow fractional reserve (FFR), particularly with multivessel disease.

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