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Coronary Artery Disease (D Feldman and V Voudris, Section Editors)

Bare Metal Stents Versus Drug Eluting Stents: Where Do We Stand in 2015?

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Opinion statement

The development of bare metal stent (BMS) was a major advancement over plain old balloon angioplasty (POBA) in the management of symptomatic coronary artery disease. BMS prevented restenosis by attenuating early arterial recoil and contraction; both seen commonly after POBA. However, the rate of clinically indicated target lesion repeat revascularization due to a process of in-stent restenosis (ISR) at 1 year remained relatively high (10 to 20 %), often due to excessive neointimal growth (Fischman et al. N Engl J Med. 331:496, 1994; Serruys et al. N Engl J Med. 331:489, 1994; Cutlip et al. J Am Coll Cardiol 40:2082, 2002). Stents with drug elution technology (DES) were developed to reduce the relatively high rate of ISR and subsequent repeat revascularization seen with BMS. Clinical trials have confirmed a reduction of as much as 50 to 70 % in target lesion revascularization by DES compared to BMS. These findings have led to the preferential use of DES in the majority of percutaneous coronary intervention (PCI). However, as DES require a longer period of dual antiplatelet therapy (DAPT) to prevent stent thrombosis, DES are not appropriate for all patients.

Introduction

History of bare metal stents

In June 1993, the US Food and Drug Administration (FDA) approved the first bare metal stent (BMS), the Gianturco-Roubin stent (GRS). The GRS was designed by Cesar Gianturco and Gary Roubin, a radiologist and interventional cardiologist. Manufactured and sold by Cook Inc (Bloomington, IN) using a flat 316-L stainless steel wire coil attached to a single longitudinal strut, the

stent was designed to be a balloon-expandable and coil-type stent. It ranged from 12 to 16 mm in length and 2.5 to 5 mm. In August 1994, the FDA approved the second BMS, the Palmaz-Schatz stent. The Palmaz-Schatz BMS was designed by Julio C. Palmaz and Richard Schatz, an interventional radiologist and cardiologist, respectively. Manufactured and sold by Cordis (Bridgewater, NJ) using 316-L stainless steel, it was designed to be a balloon-expandable and slotted tube-type stent. Unlike GRS, only one stent length (15 mm) was manufactured with diameters ranging from 3 to 5 mm.

The development of BMS was a major advancement over POBA in the management of symptomatic coronary artery disease. Acute vessel closure and restenosis have been the major limitations of POBA. Early studies with BMS revealed that they were highly effective for treating and/or preventing acute or threatened vessel closure and thereby reducing the incidence of emergency bypass surgery [1–3]. Two randomized trials, the Benestent study [4] and the Stent Restenosis Study (STRESS) [5], demonstrated that the use of BMS in native vessels reduced angiographic restenosis by approximately 30 % as compared with conventional POBA. The use of BMS produced a larger lumen diameter than POBA with respect to acute gain and net gain, seen in follow-up. This resulted in less restenosis.

Bare metal stents versus coronary artery bypass grafting

When treated with POBA, 37 % of patients in the Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI) [6] and 54 % of patients in the Bypass Angioplasty Revascularization Investigation (BARI) trial [7] needed a second revascularization. Subsequently, the use of BMS, instead of POBA, was compared with coronary artery bypass grafting (CABG) for the treatment of multivessel coronary artery disease in the Arterial Revascularization Therapies Study (ARTS) [8]. No differences were noted in the rates of death, stroke, or myocardial infarction (MI) at 1-year follow-up. Event-free survival was better in the surgery group than in the stent group (87.8 vs 73.8 %), and fewer patients in the surgery group required a second revascularization procedure (3.5 vs 16.8 %). As seen in ERACI and BARI, patients with diabetes and those who received incomplete surgical revascularization did worse. The initial cost savings of BMS compared with CABG was $4212 which was reduced to $2973 after 1 year, due to the need for repeat revascularization.

The Stent or Surgery (SoS) trial compared BMS with CABG in similar patients and reported a 21 % 2-year target vessel revascularization rate in patients who received BMS versus 6 % in CABG patients [9]. Death and MI rates were similar in the 2 groups; however, the SoS trial had a higher noncardiac death among patients receiving BMS. This has been thought to be attributable to a type II error of the study. Both the SOS and ARTS trials point to the safety of BMS in treatment of multivessel disease. The rates for repeat target vessel revascularization have been halved with BMS compared with POBA, and overall mortality was low, when the noncardiac deaths are discounted. As in the aforementioned trials, patients who received PCI in the New York Cardiac Registry, as initial therapy, had a higher incidence of target vessel revascularization (35.1 %) than those who underwent CABG (4.9 %). A total of 59,314 patients with multivessel disease who underwent either CABG (37,212) or PCI with BMS (22,102) were identified, and the reported endpoints were repeat revascularization and survival rates within 3 years. Using unadjusted survival curves, the registry data in patients who had 2-vessel disease without left anterior descending (LAD) involvement, PCI offered a small survival benefit. In patients who had 2-vessel disease with proximal LAD disease, the 2 procedures had similar mortalities (91.4 % for CABG vs 91.2 % for PCI). The survival benefit of CABG over PCI was seen in patients who had 3-vessel disease with proximal LAD disease [10].

History of drug eluting stents

DES consists of a metallic stent backbone, an antiproliferative drug, and a polymer that serves as the vehicle for the drug and also controls the drug release rate. Its design is to inhibit excessive neointimal growth, a major cause of restenosis. Since each DES is unique, differences may be observed with respect to deliverability, efficacy, and safety.

BMS versus DES

DES have been shown to reduce the need for repeat revascularization procedures compared with BMS [11, 12]. A meta-analysis of 76 trials with 117,762 patient years of follow-up in patients undergoing PCI showed that when compared with BMS, each DES reduced restenosis, but the magnitude varied by type of DES used [13]. However, the 2011 ACCF/AHA/SCAI Guidelines for PCI only considered DES as a useful alternative to BMS (class I) and considered the implantation of BMS if

the patient is not likely to be able to tolerate and comply with prolonged DAPT or this cannot be determined before stent implantation, a class III indication. The 2013 ACCF/AHA guidelines for patients presenting with ST-elevation myocardial infarction (STEMI) [14] left the choice of the stent type at the operator's discretion, only advocating for a BMS for high bleeding risk, inability to comply with 1 year of DAPT, or anticipated invasive or surgical procedures in the next year. There is mounting evidence regarding the preferential use of BMS beyond the previously mentioned contexts [15] as well as long-term benefit and lower risks with DES [16].

The first double-blind randomized study comparing BMS to DES was the RAVEL trial [17], which compared the sirolimus-eluting CYPHER stent (SES) with its noncoated counterpart, the BX velocity stent, in 238 patients with de novo lesions. At 6 months, the degree of neointimal proliferation, and binary instent restenosis was significantly lower in the sirolimus-stent group than in the BMS (control) group. None of the patients in the sirolimus stent group had restenosis, while 23.4 % of the patient in the control group ($p<0.001$) developed binary restenosis. The overall rate of major adverse cardiac events was significantly lower in the sirolimus-stent group than in controls at 1 year, primarily owing to a higher rate of target vessel revascularization in the control group.

The paclitaxel-eluting stent (PES) was initially compared to BMS in the TAXUS trials [17]. In each of these trials, TAXUS DES resulted in lower target vessel revascularization rates when compared to BMS but greater lumen loss than in CYPHER DES as seen in RAVEL. Each subsequent TAXUS study included more complex lesions and higher-risk patients, but the results were relatively consistent with the TAXUS stent across all lesion groups. Also, the paclitaxel-eluting stent platform had been slightly altered and tested in the PERSEUS trial. This trial showed lower rates of major adverse cardiac events, target lesion failure, and myocardial infarction compared with the earlier-generation TAXUS stents.

Everolimus eluting DES

The everolimus-eluting stent (EES) is available under separate names, XIENCE V and PROMUS, and has undergone several iterations since their initial rollout. EES was shown to be superior to its bare metal counterpart in terms of in-stent late loss and ISR in the original SPIR IT trial [18]. Subsequently, the EES was then compared with other drug-eluting stents in the SPIRIT II, III, and IV trials [19]. In these trials, a significant advantage in terms of target lesion revascularization, combined cardiac endpoints, and early and late stent thrombosis emerged for the EES stent over the paclitaxel-eluting stent. The SPIRIT trials resulted in a major shift toward EES use and away from paclitaxel-eluting stent use. In the RESET trial, target lesion revascularization was similar for patients treated with EES and sirolimus-eluting stents 1-year postprocedure [20].

In a meta-analysis of 42 trials with 22,844 patient years of follow-up, EES were the most efficacious and safer in patients with diabetes when compared to BMS and paclitaxel- or sirolimus-eluting stents. DES consistently demonstrated superiority in reducing ischemic coronary events in diabetics when compared to BMSs. Although EES appear to demonstrate the greatest relative efficacy advantage among DES, patient and lesion types were not always comparable across trials [21]. In a comparison of intrastent conditions in patients with ST-segment elevation myocardial infarction and stable angina using optical coherence tomography and angioscopy 12 months after implantation, second-generation EES was shown to promote favorable healing [22].

Zotarolimus-eluting DES

The first zotarolimus-eluting stent (ZES) was marketed as the endeavor stent, which was studied against its bare metal counterpart in the ENDEAVOR trials [23]. The trials showed a reduction in target lesion and vessel revascularization for the ZES compared to the BMS. Subsequent ENDEAVOR trials compared the ZES to paclitaxel DES. Over 5 years, significant differences in death, myocardial infarction, and composite endpoints favored treatment with ZES [24].

EES versus ZES

Multiple randomized trials and one registry have found that EES and resolute zotarolimus-eluting stent (R-ZES) are comparable in terms of efficacy and safety. The Resolute All Comers trial randomly assigned 2292 patients with either stable coronary artery disease or an acute coronary syndrome to either the R-ZES or an EES [25]. There was no significant difference in the rate of the primary endpoint of target vessel failure over 12 months between the R-ZES and EES. The R-ZES was also noninferior to the EES regarding the degree of ISR or in-stent late lumen loss. There was no significant difference between the R-ZES and EES groups in either the composite patient-related outcome of all death, MI, or revascularization or the stent-related outcome of target lesion failure over 2 years. The rate of target lesion revascularization and definite or probable stent

thrombosis was not significantly different in the two groups at 1 year. Subsequently, the TWENTE trial randomly assigned 1391 patients with complex, stable coronary artery disease or non-ST elevation acute coronary syndromes to R-ZES or EES [26]. The rates of target vessel failure, definite or probable stent thrombosis, and death from cardiac causes were low and similar for the two groups. The DUTCH PEERS study randomized 2371 patients with both stable and unstable disease to R-ZES or EES [27]. The primary combined end point of target-vessel failure and efficacy at 12 months was similar in both groups.

When comparing the platinum chromium EES and cobalt chromium R-ZES, the HOST-ASSURE trial evaluated the difference on an all-comers randomized cohort. The primary end point, one-year target lesion failure was equivalent in the two groups [28•]. Over 5000 patients enrolled in the EXCELLENT and RESOLUTE-Korea registries who received either R-ZES or EES for unrestricted indications revealed similar results [29]. There was no significant difference in the rate of the primary combined outcomes and stent thrombosis.

Comparison of BMS and DES in saphenous vein grafts

Saphenous vein graft (SVG) degeneration leading to stenosis has high incidence of almost 50 % at 10 year [30]. SVG stenosis-associated clinical ischemia accounts for up to 15 % of the total coronary interventions performed. Saphenous Vein De Novo (SAVED) was one of the first prospective trials that compared POBA with BMS in de novo SVG lesions. The use of BMS was associated with better immediate procedural outcomes with no increase in complications. Even though there was no statistical difference in the rate of restenosis, use of BMS resulted in improved composite endpoint of freedom from death, MI, repeat CABG, and target lesion revascularization (TLR) at 6-month follow-up [31]. Long-term results of SVG interventions using BMSs have been discouraging. This is related to combination of severe aggressive degenerative disease in the grafts leading to higher rates of ischemia and associated TLR and TVR. The advent of DES has gradually improved outcomes of PCI to the SVG.

Stenting of SVG trial (SOS) was a randomized trial comparing paclitaxel eluting stent (PES) with BMS for SVG interventions. This showed that the PES was associated with less binary ISR and TLR (5 vs 28 %, $p=0.003$) with comparable cardiac mortality between the two groups. Similarly, the prior studies have demonstrated lower ISR in patients treated with PES and SES compared to BMS [32]. However, there was heightened concern for late stent thrombosis with PES over a 3-year follow-up period, leading to higher mortality seen in the DELAYED RRISC trial [33]. This finding is not consistent with the results of other trials. In the blinded randomized ISAR-CABG trial, DES including PES and SES were found to be superior to BMS with regards to major adverse cardiac events (MACE) and ischemia-driven TLR and TVR with no increased risk of mortality or stent thrombosis [34]. In a meta-analysis of 23 studies by Wiisanen et al., similar overall net benefit in favor of DES in improving mortality, MACE, and TVR was demonstrated [35]. In a nonrandomized propensity matched retrospective study by Aggarwal et al., patients treated with DES at VA hospitals had lower mortality (HR 0.72; 95 % CI 0.57 to 0.89) and similar rates of myocardial infarction over 2-year follow-up [36]. Based on the available evidence, DES, when compared to BMS, are as safe and have better outcomes including reducing TVR when treating SVG lesions.

Comparing BMS and DES in chronic total occlusions

Treatment of chronic total occlusions (CTO) of the coronary arteries is a very selective subgroup associated with procedural challenges, lower success rate, and worse long-term vessel patency and clinical outcomes [37]. There are very few randomized controlled trials comparing different stent types when used in CTO cases. PRISON II was a randomized trial that showed lower ISR with the use of SES versus BXveolcity BMS [38]. Only 100 patients were enrolled in each arm. In another small RCT conducted in Europe, when SES was compared with BMS, SES was associated with lower binary ISR (9.8 vs 67.7 %, $P<0.001$) and overall MACE events driven by lower TVR [39]. Long-term patency after CTO PCI is dependent on stent length, vessel diameter, and CTO techniques used, subintimal versus intraluminal [40]. These factors likely explain the improved outcomes seen with use of DES as compared with BMS. While the first generation DES is superior to BMS, there is limited data comparing the new generation DES with BMS. In a noninferiority randomized control trial comparing second generation ZES and SES, Park et al. showed that the second-generation ZES was found to be noninferior in terms of efficacy and safety endpoint over a 9-month follow-up period [41]. Similar favorable results for DES over BMS are supported by more recent meta-analysis and retrospective data as well [42, 43]. Given the current data, if clinically appropriate, the recommendation is to use DES for CTO PCI to achieve long-term vessel patency rates and reduce risk of future TVR.

Comparing DES and BMS for ST elevation myocardial infarction

Primary PCI with stent placement is the standard of care for patients with ST-elevation myocardial infarction (STEMI) patients. There are a number of factors that influence the choice of stents in treating these patients, the incidence of ISR and more importantly stent thrombosis. The latter is especially crucial as PCI in ACS patients may be associated with a higher than usual risk of acute stent thrombosis leading to a drastic increase in mortality and morbidity [44]. There have been several studies, most notably by Vink et al. and Brodie et al. which have demonstrated a higher rate of very late stent thrombosis with the use of fist generation DES, namely PES and SES [45, 46]. In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, there was a trend toward higher rates of very late stent thrombosis in a landmark analysis from after the first year of follow-up, up to 3 years (PES 1.7 % vs BMS 0.9 %, $P=0.12$). More recent data published by Garg et al. comparing BMS with DES in STEMI patients revealed that the newer generation had rates of stent thrombosis similar to the early generation DES but lower than BMS [47]. The newer generations of DES have shown promising results as seen in the data published from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). In 34,147 patients treated for STEMI in Sweden, patients treated with a newer generation DES maintained a lower rate of stent thrombosis for 3 years of follow-up as compared with the older generation DES and BMS (1.3, 2.1, and 2 %, respectively) [48]. Pooled data from the Clinical Evaluation of the Xience-V stent in Acute Myocardial Infarction (EXAMINATION) and Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE-AMI) trials revealed a similar reduction in incidence of stent thrombosis with new generation DES as compared with BMS (RR 0.35; 95 % CI 0.16 to 0.75; $p=0.006$) while maintaining their effectiveness with reduced MACE events including TLR (RR 0.33; 95 % CI 0.20 to 0.52; $p<0.0001$) [49•]. Based on the recently published literature, it does appear that the use of DES offers a safer and more efficacious choice for treatment of patients with STEMI.

Future technology

A clinical trial for a novel concept coronary stent started enrolling patients in the USA: the COBRA PzF™ (CeloNova BioSciences Inc., San Antonio, TX) coronary stent system. The clinical trial, named PzF Shield, is enrolling in a nonrandomized single arm trial. The primary endpoint will be the incidence of Target Vessel Failure (TVF) within 270 days. What is unique about the COBRA PzF is the coating on the stent; it is a nano-thin coating of Polyzene®-F polymer, approximately 100 times thinner than the polymers found on currently available drug-eluting stents. The implications of this are faster and more natural healing of the artery and reduce the need for long-term DAPT, in effect equaling the outcomes of DES without the need for long-term DAPT. The COBRA PzF currently has the CE Mark and is available for sale in European and other OUS markets. The safety benefit of lower stent thrombosis is a major potential advantage to the COBRA stent. This current study of only 300 patients is not sufficiently powered to measure this incidence.

Another technology in its infancy is bioresorbable stents and bioresorbable polymers. Most bioresorbable stents are made of polylactic acid, a naturally dissolvable material that is used in medical implants such as dissolving sutures. The drawbacks of using bioresorbable stents include recoil after expansion, stent thickness causing maneuverability and crossing issues, difficulty visualizing a nonmetallic stent on fluoroscopy, and stents not crimping firmly on delivery balloons. However, the

advantage is not implanting a durable metal prosthesis. Since the stent disappears, it eliminates the cause of potential inflammation that may lead to late-stent thrombosis and restenosis. Once the stent dissolves, it restores the vessel to a natural state of vasoconstriction and vasodilatation. The disappearance of the device also leaves open all options if future interventions are needed. First-generation devices are currently available outside the USA; however, bioresorbable polymers are yet to be released commercially. In a recent meta-analysis, bioresorbable biolimus stents were associated with superior clinical outcomes compared with BMS and first-generation DES. However, similar rates of cardiac death/MI, MI, and TVR as compared with second-generation DES with higher rates of definite ST than CoCr-EES were observed.

Discussion

There is an ongoing debate regarding the guidelines' position from the choice of stent type in the setting of PCI in view of recent literature showing better outcomes and even better risk profile with DES (especially newer generation ones) compared to BMS. Though DES have demonstrated lower restenosis rates and target vessel revascularization in comparison to BMS [50, 51], stent thrombosis and its substantial mortality risk in patients receiving a DES are still a concern [52–55]. Reduced mortality rates with DES use in primary PCI have been documented in state registries such as the Massachussets registry [56] but were limited by the stent selection and the differential in clopidogrel duration. Recent meta-analyses have concluded that in patients with STEMI, especially as the transition has been made from first to second and now third generation DES, this movement has been associated with a substantial decrease in the risk of target vessel revascularization without compromising safety. Depending on stent type, the added advantage of substantial reduction in the risk of stent thrombosis was noted when compared to BMS.

The other facet of the controversy surrounding stent choice is the compliance with DAPT and its duration. In this instance as well, recent literature favors a new outlook on this aspect of PCI. In the PARIS registry-based prospective observational study [57], Mehran et al. found no statistically significant difference in the rate of adverse events in patients who had discontinued DAPT after 6 months from PCI. Though early risk for events due to disruption was substantial, it was irrespective of stent type. The OPTIMIZE trial [58] reported that in patients with stable coronary artery disease or low-risk ACS treated with zotarolimus-eluting stents, 3 months of DAPT was noninferior to 12 months for adverse events, without significantly increasing the risk of stent thrombosis. In similar fashion, the pivotal RESOLUTE US trial [59] indicated low stent thrombosis rates for patients who interrupted or discontinued DAPT any time after first 30 days. Finally, the results of the DAPT trial [60•] indicate that prolonged duration of DAPT up to 30 months following index PCI with a DES results in lower stent thrombosis and recurrent MIs compared with a 12-month duration of DAPT, although

bleeding and all-cause mortality were higher with prolonged therapy. The BMS subset shows a less impressive treatment effect, although the *p* value for interaction between DES versus BMS was not significant. Both stent thrombosis and spontaneous MIs were reduced in DES patients, but not in BMS patients.

Conclusion

BMS played a very important role after POBA to allow for sustainable results after PCI. DES subsequently capitalized on even further improvements in TVR and TLR, however, adding the risk of late and very late stent thrombosis given its slower rate of endothelialization. Third-generation DES have significantly improved upon the risk of stent thrombosis by varying the polymer and elution time of the drug; however, the risk of stent thrombosis remains insignificantly higher than that of BMS. With bioabsorbable stents demonstrating noninferiority and nondrug coated, nano polymer-based BMS showing signs of potential superiority, the debate between BMS and DES is far from over. Duration and compliance of DAPT will remain a very important factor in choosing stent type during PCI; however, understanding the evidence-based application of this choice may be of even more interesting in today's age of third-generation DES.

Compliance with Ethics Guidelines

Conflict of Interest

Perwaiz M. Meraj reports grants and personal fees from Abiomed Inc., grants and personal fees from Medtronic Inc., grants and personal fees from Boston Scientific Inc.
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Avneet Singh declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

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In this Randomized trial involving 3755 all comers, platinum chromium (PtCr)-based everolimus-eluting stent (EES) was found to be noninferior to the cobalt chromium (CoCr)-based zotarolimus-eluting stent (ZES) subjects receiving percutaneous coronary intervention (PCI) defined as the composite of cardiac death, nonfatal target vessel–related myocardial infarction, and ischemia-driven target lesion revascularization.

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