An Era of Coronary Stents

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Abstract
The majority of percutaneous coronary intervention cases are performed using drug eluting stents. Trials have consistently demonstrated lower rates of in stent restenosis and repeat revascularization with drug eluting stents when compared with bare metal stents. Stent technology has improved over the decade with changes in the thickness of stent struts, polymer coating and ease of stent delivery to the desired location. Furthermore shorter duration of antiplatelet therapy appears to be a promising option with the biolimus A9 polymer free drug carrier stent. This is particularly beneficial in patients who are deemed to be at high risk of bleeding such as those who are prescribed coexisting anticoagulation. The development of the biodegradable stent allows the stent to be resorbed over time so that the stent is no longer present in the vessel thus avoiding the problems seen with conventional stents such as in stent restenosis.

Keywords: Percutaneous coronary intervention; Drug eluting stents; Bare metal stents; Restenosis rates; Biodegradable polymers

Introduction
Target lesion revascularization is reduced by 50-70% with drug eluting stents (DES) when compared with bare metal stents (BMS). This has led to the increased use of DES in patients. DES has an antiproliferative drug coating inhibiting neointimal growth which is a cause of restenosis. There are several types of DES available and vary in the ability to prevent restenosis and stent thrombosis due to changes in the drug and polymer coating. Unlike the BMS, DES requires the prescription of prolonged dual anti platelet therapy (DAPT) to reduce the rates of stent thrombosis. The duration of DAPT can however be reduced to 3-6 months in certain circumstances such as those who require surgery or patients at increased risk of bleeding [1]. First generation DES includes those that release sirolimus or paclitaxel on a stent platform of stainless steel.

These demonstrated lower restenosis rates when compared to BMS. However late stent thrombosis was a concern with the first generation DES and these have been largely been replaced by second generation DES including those that release everolimus or zotarolimus on a stent platform of cobalt chromium. Newer third generation stents include polymer free stents or those that are resorbed over time so that the stent is no longer seen in the vessel.

Discussion
The decision to use a BMS or DES should be individualized. Several factors need to be considered including the risk of restenosis, stent thrombosis and bleeding with prolonged DAPT use. Studies have shown that there is no difference in the rates of early (<30 days) and late (between 30 days to 365 days) stent thrombosis between DES and BMS. However, very late stent thrombosis (>1 year) increases with DES [2-5]. Second generation DES have shown lower rates of in stent restenosis and stent thrombosis when compared to first generation DES [6,7]. Stent thrombosis is significantly reduced by the use of DAPT. The efficacy of antiplatelets however, is affected by patient compliance. Certain P2y12 inhibitors such as clopidogrel require conversion to its active form by the use of several cytochrome p450 enzymes. A lack of the enzymes may render clopidogrel ineffective which may result in stent thrombosis [8-10].

Stent thrombosis and restenosis can also be reduced by using intravascular ultrasound guided stent implantation to ensure that stents are well deployed and opposed to the vessel wall [11]. Target vessel revascularization is influenced by the presence of diabetes mellitus, use of longer stents and stent deployment in smaller vessels especially with the use of BMS [2,12,13]. In a study by Yeh et al. [14] target vessel revascularization at 1
First generation drug eluting stents and bare metal stents

Sirolimus and paclitaxel eluting stents are first generation DES. There were initial concerns about increased mortality rates, myocardial infarction and stent thrombosis with the first generation DES when compared to BMS. In an analysis of 18,023 patients who had percutaneous coronary intervention (PCI) with a BMS or a sirolimus/paclitaxel eluting stent outcomes were assessed over a 4 year period. Mortality rates were similar in the three groups. Sirolimus eluting stents were associated with the lowest risk of myocardial infarction p=0.030 versus bare metal stent, p=0.045 versus paclitaxel eluting stents. The risk of definite stent thrombosis at >30 days was increased with paclitaxel eluting stents p=0.017 versus bare metal stent p=0.041 versus sirolimus eluting stents. Target lesion revascularization was commonly encountered with paclitaxel eluting stents than with sirolimus eluting stents, p=0.0021. Sirolimus eluting stents therefore performed better than BMS and paclitaxel eluting stents [2].

Sirolimus eluting stents and bare metal stents

Direct head to head trials with the sirolimus eluting stent and BMS have shown reduced rates of restenosis with sirolimus eluting stents. In a meta analysis of 1748 patients enrolled in four randomized trials the safety of sirolimus eluting stents were compared with BMS with regards to survival at 4 years. The survival rate at 4 years was 93.3% in the sirolimus stent group and 94.6% in the bare metal stent group (P=0.28). Rates of myocardial infarction and stent thrombosis were similar in the two groups [12]. In a further analysis of 14 randomized trials the rates of death, stent thrombosis, myocardial infarction and revascularization rates were assessed with both stent types. The combined risk of death or myocardial infarction was similar for both groups. There was however a significant reduction in the combined risk of death, myocardial infarction, or re-intervention associated with the use of sirolimus eluting stents. Rates of stent thrombosis did not differ between both groups early in follow up however after the first year there was a slight increase in the rate of stent thrombosis with sirolimus eluting stents [13].

Everolimus eluting stent and paclitaxel eluting stent

In a randomized study of 3687 patients the second generation everolimus eluting stent was compared with the first generation paclitaxel eluting stents. The 1 year composite rate of target lesion failure, defined as cardiac death, target vessel myocardial infarction, or ischemia driven target lesion revascularization was analysed. Everolimus eluting stents were superior to paclitaxel eluting stents with regards to the composite primary end point; 4.2% vs. 6.8% respectively P=0.001. There was a significant reduction in the 1 year rate of ischemia driven target lesion revascularization with everolimus eluting stents (P=0.001). Rates of myocardial infarction and stent thrombosis were also lower with the everolimus eluting stent than with the paclitaxel eluting stent 1.9% and 3.1% P=0.02 respectively for myocardial infarction; 0.17% and 0.85% P=0.004 for stent thrombosis. Therefore the everolimus eluting stent was superior to the paclitaxel eluting stent as there was a significant reduction in target lesion failure and stent thrombosis at 1 year [6].

Everolimus and bare metal stents

Sirolimus eluting stents have been shown to be superior to paclitaxel eluting stent [15] and therefore have generally used as the standard to compare with second generation stents. In the BASKET trial the efficacy of first generation SES (sirolimus eluting stent) and BMS placed in large coronary arteries was assessed. The efficacy of sirolimus eluting stents with the second generation everolimus eluting stent was also assessed. At 2 year follow-up, there were no significant differences in either of the groups for the primary end point of death from cardiac causes or nonfatal myocardial infarction. The primary end point occurred in 2.6% of patients receiving the sirolimus eluting stent; 3.2% in the everolimus group, and 4.8% in the BMS group. Stent thrombosis rates were also similar in all 3 groups. The rates of target vessel revascularization was significantly reduced amongst patients receiving a DES when compared with a BMS, 3.7% for sirolimus eluting stents, 3.1% for everolimus eluting stents and 8.9% for BMS. In patients requiring PCI of large coronary arteries, the rates of death and myocardial infarction were similar amongst all groups. Similar reductions in the rates of target vessel revascularization were seen with both DES [16].

In the most recent trial of DES and BMS the NORSTENT study assessed long term outcomes in 9013 patients undergoing PCI. Second generation DES, zotarolimus or everolimus eluting stent were compared with BMS. At 6 years the primary composite outcome of death and non fatal myocardial infarction occurred in 16.6% of patients receiving DES and 17.1% receiving BMS (P=0.66). Repeat revascularization was encountered in 16.5% and 19.8% respectively (P<0.001). Stent thrombosis rates were lower with DES versus BMS; 0.8% and 1.2% respectively (P=0.049). Although rates of stent thrombosis were lower in the DES group the incidence of overall stent thrombosis has reduced over the decade due to improvements in stent design. Quality of life measures such as the presence of anginal symptoms, frequency of angina and physical limitations were similar amongst both treatment arms [17].

Zotarolimus and everolimus eluting stents

Second generation zotarolimus and everolimus eluting stents have shown reduced rates of restenosis, however, it is unclear whether there are differences in efficacy and safety between the two types of stents. In a randomized study, 2292
patients were assigned to treatment with either zotarolimus or everolimus eluting stents. The primary end point of target lesion failure, defined as a composite of death from cardiac causes, myocardial infarction or clinically indicated target lesion revascularization within 12 months was assessed. Repeat angiography was performed in 20% of patients at 13 months to assess the extent of in stent stenosis. The zotarolimus eluting stent was non inferior to the everolimus eluting stent with respect to the primary end point, which occurred in 8.2% and 8.3% of patients, respectively. The rate of stent thrombosis was 2.3% in the zotarolimus stent group and 1.5% in the everolimus stent group (P=0.17). In-stent late lumen loss was 0.27±0.43 mm in the zotarolimus eluting stent group and 0.19±0.40 mm in the everolimus stent group (P=0.08). There were no significant differences in the primary outcomes with both stent types [7].

**Third generation stents**

Third generation stents include the promus premier stent on a backbone of cobalt chromium, the biolimus A9 stent and bioresorbable stents. In the LEADERS free trial the biolimus A9 polymer free drug coated stent demonstrated superiority over the gazelle BMS in patients who were at increased risk of bleeding but required PCI. The biolimus A9 stent is polymer free and elutes urimolimus in the coronary vessel wall within 1 month of implantation. Patients were randomized to receive the gazelle BMS or the biolimus A9 stent followed by 1 month of DAPT. The primary end point of death, myocardial infarction and stent thrombosis occurred in 12.9% of patients who received a BMS and was significantly lower in the patients who received the biolimus A9 stent at 9.4%. Target lesion revascularization was also lower with the biolimus A9 stent, 5.1% and 9.8% with a BMS.

Therefore, in patients who are at high risk of bleeding such as those who require concomitant anticoagulation for conditions such as atrial fibrillation the biolimus A9 appears to be a promising option [18]. It is important to note that over 60% of patients in the trial were deemed to be at increased risk of bleeding based on being above > 75 years of age. In real life practice shorter duration of DAPT is not often prescribed based on age alone unless there are other factors to support increased bleeding risk. Further trials with the biolimus A9 stent and the promus everolimus eluting stent have demonstrated non inferiority. In the NOBORI trial the rate of target vessel revascularization at 1 year was the same with both stent types. Definite stent thrombosis was also similar amongst groups, 0.25% for biolimus and 0.06% for promus p=0.18 [19]. Therefore, the biolimus A9 stent was non inferior to the promus everolimus eluting stent.

Newer stents such as the bioresorbable scaffold stent elutes everolimus and has thicker stent struts and take 4-5 years before it is fully resorbed. It is believed to reduce restenosis as stent struts are resorbed over time leaving no substrate for restenosis. The bioresorbable stent has shown similar rates of target lesion revascularization, target lesion failure, myocardial infarction and death when compared to the everolimus eluting metallic stent. However, definite or probable stent thrombosis rates were higher in patients treated with the bioresorbable stent specifically within the first 30 days of deployment [20]. The stent maybe a viable option in younger patients who may potentially require a coronary artery bypass graft surgery in the future where a standard DES may prevent optimal graft positioning in the vessel.

**Conclusion**

The decision to implant a stent needs to be individualized taking into account the risk of stent thrombosis, restenosis and bleeding with prolonged dual antiplatelet therapy use. In general DES is superior to BMS in reducing the rates of repeat revascularization. The biolimus a9 stent maybe considered in patients at increased risk of bleeding where antiplatelet therapy can be shortened to 1 month and the bioresorbable scaffold stent may be suited for younger patients. Further trials however are being conducted to assess the safety and efficacy of the bioresorbable stent.

**References**


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