Drug-eluting Stents

What Would Be the Ideal Drug-eluting Stent for Managing Patients with Long Lesions?

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Abstract

Drug-eluting stents (DES) substantially reduce the risk of restenosis, particularly in complex coronary disease. Their use is now standard in demanding anatomy, including in long lesions, which represent an increasing proportion of percutaneous coronary intervention (PCI) cases. However, long lesions pose a number of procedural and clinical challenges for DES, specifically stent deliverability, stent overlap and an increased risk of restenosis, peri-procedural myocardial infarction, geographical miss and stent thrombosis. The ideal DES for long lesions would incorporate a number of specific design characteristics to meet these challenges, including low late loss to minimise restenosis risk, thin struts to enhance deliverability and minimise risk of peri-procedural infarction and the availability of long lengths to minimise overlap and avoid geographical miss. It is clear from a knowledge of their properties, and from available data on DES performance in long lesions, that some currently available DES have superior design characteristics and clinical outcomes in the setting of diffuse disease. An awareness of these issues is essential for the practising interventional cardiologist in treating long lesions in routine clinical practice.

Keywords

Percutaneous coronary intervention, angioplasty, drug-eluting stents, long lesions, restenosis, stent deliverability

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The introduction of coronary stents in the late 1980s improved outcome over balloon angioplasty via a reduction in acute vessel closure, prevention of vessel recoil, increase in acute gain and a lower rate of clinical restenosis. However, in-stent restenosis (ISR), caused by smooth-muscle cell proliferation and migration, leading to neointimal hyperplasia, remains the Achilles’ heel of bare-metal stents (BMS). The development of drug-eluting stents (DES), which release antiproliferative drugs into the vessel wall to inhibit neointimal hyperplasia, has revolutionised percutaneous coronary intervention (PCI), dramatically reducing the incidence of ISR and target lesion revascularisation (TLR) and permitting the treatment of more complex and extensive coronary artery disease, including diffuse or long lesions.

Long lesions account for approximately 20% of contemporary PCI cases, and present specific challenges for drug-eluting stenting. In this article we describe the difficulties encountered in the treatment of long lesions using DES. We discuss how the characteristics and design of DES could be adapted to overcome these challenges and to deliver an optimal outcome. Finally, we relate these observations to contemporary DES, and discuss the evidence for the performance of the different commercially available DES in the setting of long lesions. For the purposes of this article we will focus on those DES with pivotal phase III randomised controlled trial data at the time of writing, namely the CYPHER sirolimus-eluting stent (SES) (Cordis, Johnson & Johnson, Miami Lakes, FL, US), the TAXUS paclitaxel-eluting stent (PES) (Boston Scientific, Natick, MA, US), the Endeavor Sprint zotarolimus-eluting stent (ZES) (Medtronic, Santa Rosa, CA, US), the Xience V (Abbott Vascular, IL, US)/Promus (Boston Scientific) everolimus-eluting stent (EES) and the Biolimus biolimus-eluting stent (BES) (Biosensors Interventional, Singapore), although emerging technologies will also be discussed.

The Role of Drug-eluting Stents in Long Lesions

Together with vessel diameter, lesion length is the most powerful factor influencing the risk of ISR. For BMS, lesion length is an independent predictor of late lumen loss, binary angiographic ISR, TLR and major adverse cardiac events (MACE: death, non-fatal myocardial infarction [MI] or target vessel revascularisation [TVR]).

The increased incidence of clinical and angiographic restenosis with longer lesions relates simply to the greater degree of arterial wall injury and consequent neointimal proliferation, and significantly limits the clinical utility of BMS in the treatment of long lesions. The dramatic reduction in restenosis associated with DES is greatest in complex disease settings in which BMS fare poorly, including long lesions. Data from randomised controlled trials and large observational registries highlight the increased risk of restenosis with longer lesions, and demonstrate a significant reduction in restenosis and TVR rates with DES use.

As a consequence, use of DES in long lesions has become standard clinical practice, supported by international guidelines.
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The Challenges of Long Lesions for Drug-eluting Stenting

Even with DES use, treatment of long lesions poses a number of specific challenges to the interventional cardiologist, including an increased risk of restenosis, peri-procedural MI, stent deliverability, geographical miss (GM) and stent thrombosis (ST). The ideal DES for long lesions needs to offer optimal performance with regard to each of these factors.

Restenosis

Although significantly lower than with BMS, angiographic and clinical restenosis rates with DES use also increase progressively with lesion length (see Figure 1).28 The ideal DES in long lesions must ameliorate restenosis risk by effectively inhibiting neointimal hyperplasia and minimising late loss, and hence delivering low rates of TLR and MACE. Late loss is a reliable discriminator of restenosis propensity between DES platforms19,20 and, despite there being a class effect, not all DES systems are equal. Late loss appears greatest with the Endeavor Sprint ZES (circa 0.62mm),21 intermediate with the TAXUS PES (circa 0.39mm)22 and lowest with the CYPHER SES (circa 0.17mm),23 the XIENCE V/Promus EES (circa 0.14mm)24 and the Biomatrix BES (circa 0.13mm).25

It could be hypothesised that those DES with lower late loss would offer superior efficacy with regard to restenosis in long lesions. Unfortunately, few studies have specifically assessed DES use in long lesions, and head-to-head data directly comparing different DES are even more limited.

The non-randomised Long DES I study compared SES and PES versus BMS in 637 patients with long lesions (mean length 34.5±13.7mm).26 ISR at six months was 6.3, 16 and 40.6% for the SES, PES and BMS, respectively (p<0.001). DES use significantly reduced TLR (3.7 versus 16.6%) and MACE (4.3 versus 19.8%) at seven months. The Long DES II study randomly compared SES versus PES in 500 patients with coronary lesions >25 mm in length.27 TLR and MACE rates at one year for lesions ≥20mm in length (n=9,10,11,12) were 0.4 and 5.4%, respectively, compared with 2.7 and 3.2%, respectively, for simple, single stent lesions ≤20mm in length.

Stent overlap, often unavoidable in the treatment of long lesions, has also been implicated as a stimulus for neointimal hyperplasia. Pooled analysis of five SES clinical trials found that stent overlap was associated with a greater degree of late lumen loss, as well as more frequent binary ISR, with both BMS and SES. However, TLR was increased only for BMS, not SES.29 Intravascular ultrasound data for overlapping stents in the TAXUS V and VI studies showed significantly less neointimal tissue growth and greater expansive remodelling with PES compared with BMS.29 Nonetheless, avoidance of stent overlap by use of long stents may enhance long-term stent patency.

Peri-procedural Myocardial Infarction

Myonecrosis following PCI is associated with an increase in late mortality, particularly in patients with moderately or highly elevated cardiac enzymes following PCI.18,19 The incidence of peri-procedural MI is significantly higher following treatment of long lesions,20,21 due principally to a greater incidence of side-branch occlusion adjacent to the stented segment, although distal embolisation causing microvascular obstruction and loss of collaterals may also contribute.22 Side-branch occlusion following stenting relates to mechanical obstruction by struts, straightening of the vessel and shifting of atherosclerotic plaque into the origin of the branch.

MACE = major adverse cardiac event; TLR = target lesion revascularisation.

**Figure 1: Randomised Controlled Trial and Registry Data of One-year Major Adverse Cardiac Event and Target Lesion Revascularisation Rates According to Lesion Length**

- **TLR**
  - Linear (TLR)
  - TAXUS V
  - TAXUS VI
  - SPIRIT II
  - SPIRIT V
  - SPIRIT VS
  - SPIRIT V

- **MACE**
  - Linear (MACE)
  - TAXUS V
  - TAXUS VI
  - SPIRIT II
  - SPIRIT V
  - SPIRIT VS
  - SPIRIT V

| Lesion Length (mm) | Mean lesion length (mm) |
|-------------------|-------------------------|
| 7                 | 9                      |
| 9                 | 11                     |
| 11                | 13                     |
| 13                | 15                     |
| 15                | 17                     |
| 17                | 19                     |
| 19                | 21                     |
| 21                | 23                     |

| One-year event rate (%) |
|-------------------------|
| 0                       |
| 2                       |
| 4                       |
| 6                       |
| 8                       |
| 10                      |
| 12                      |
| 14                      |
| 16                      |
| 18                      |
| 20                      |

| Mean lesion length (mm) |
|-------------------------|
| 7                       |
| 9                       |
| 11                      |
| 13                      |
| 15                      |
| 17                      |
| 19                      |
| 21                      |
| 23                      |

**Lesion Length**

**Target Lesion Revascularisation Rates According to**

**Data of One-year Major Adverse Cardiac Event and**

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Regions of stent overlap in particular predispose to mechanical compromise of the side-branch ostium, and although overlapping SES or PES appears to be a feasible and effective technique for treating long lesions, it is associated with a significant increase in peri-procedural non-Q-wave MI.\textsuperscript{21} The greater strut/polymer thickness of DES may increase the likelihood of side-branch occlusion and peri-procedural MI compared with BMS. In the TAXUS V study, the incidence of peri-procedural MI was 5.1% with PES compared with 3.6% in the BMS arm; for overlapping stents in particular, 30-day MACE rates were significantly higher with PES (8.3 versus 3.3%; \(p=0.047\)).\textsuperscript{37} Some investigators have suggested that webbing of the polymer with the TAXUS PES may also have contributed to side-branch obstruction and peri-procedural MI in this study.

Newer-generation DES with reduced strut/polymer thickness may result in less side-branch occlusion and peri-procedural MI than seen with the first-generation devices. The Xience V/Promus EES (strut thickness 88.6µm), the Endeavour ZES (91µm) and the Biomatex BES (112µm) have substantially thinner struts than both the CYPHER SES (152.6µm) and TAXUS Express PES (148µm). Post hoc analysis of 1,216 patients in the ENDEAVOR IV study showed a reduction in side-branch occlusion with ZES use compared with PES (2.2 versus 4.8%; \(p=0.032\)), with an associated reduction in the incidence of peri-procedural non-Q-wave MI (0.5 versus 2.2%; \(p=0.007\)). Side-branch occlusion was identified as an important predictor of peri-procedural MI, and independently correlated with use of PES.\textsuperscript{38} Similarly, in the ENDEAVOR III study, the occurrence of in-hospital non-Q-wave MI was significantly lower with ZES compared with the CYPHER SES (0.6 versus 3.5%; \(p=0.004\)).\textsuperscript{39} The SPIRIT III study further supported a reduction in peri-procedural MI with thinner stent struts, showing fewer peri-procedural events with the Xience/Promus EES compared with the TAXUS Express PES.\textsuperscript{40} The Biomatex BES reduces the thickness of the strut/polymer complex by application of the polymer to the abluminal surface only, while the next-generation Nevo stent (Cordis, Johnson & Johnson) employs a polymer only within wells drilled into the stent struts. Such novel stent designs may further protect against the risk of side-branch occlusion.

The availability of long lengths to minimise the need for overlap would also counter the risk of side-branch occlusion. The longest conventional stents currently manufactured are the TAXUS Liberté Long and the Xience Prime, both up to 38mm in length. The XTENT Custom NX DES (XTENT, Inc., CA, US) is a customisable 60mm stent with a biodegradable biolimus-eluting polymer consisting of multiple interdigitated 6mm cobalt-chromium stent segments, allowing the physician to tailor the stent precisely to lesion length and avoid the problem of stent overlap. This device may have a specific role in very long lesions; early results from the CUSTOM II trial are promising, with in-stent late loss of 0.22mm and TLR rates of 4%.\textsuperscript{41}

Deliverability

Deliverability is always a major factor affecting choice of DES, but is of particular importance in the treatment of long lesions, in which tortuosity and calcification are more frequently encountered and where by definition delivery of longer stents is required. Deliverability is influenced by the profile, pushability and flexibility of the delivery catheter and balloon, as well as by the thickness of the stent struts, the design of the stent framework, the polymer thickness and the profile of the crimped stent. All of these factors differ between the various commercially available DES. An open-cell stent design (such as the Endeavor ZES) has greater flexibility, which may enhance deliverability in contrast to an often more rigid closed-cell design (such as the CYPHER SES). Strut thickness is significantly lower with the newer-generation Endeavor ZES and Xience/Promus EES, in which the use of a cobalt-chromium alloy permits thinner struts without loss of radial strength. The Xience/Promus EES has the lowest crimped stent profile of 1.06mm, compared with 1.2mm for the TAXUS PES and the CYPHER SES and 1.3mm for the Endeavor ZES and the Biomatex BES.\textsuperscript{42}

Finally, the unique modular design of the Endeavor stent, consisting of interconnected sinusoidal rings (rather than a slotted tube), allows improved flexibility and may also enhance deliverability. In the ENDEAVOR III and IV studies, procedural success rates were higher with the Endeavor ZES compared with both the CYPHER and the TAXUS stents.\textsuperscript{43,44}

Geographical Miss

GM refers to the failure to fully cover an injured or diseased arterial segment during PCI. GM may result from incomplete coverage of a diseased segment due to residual disease at the stent margins or failure to overlap multiple stents, or may be a consequence of balloon injury outside the stented segment. GM is an important predictor of restenosis and myocardial infarction, and is more frequently encountered in patients with long lesions.\textsuperscript{45} In the STLLR study, GM was observed in as many as 48% of patients,\textsuperscript{46} and was related to balloon injury in 54%, uncovered disease in 32% and both in 14% of procedures. TVR (6.1 versus 2.6%; \(p<0.001\)) and MI (1.2 versus 0.2%; \(p=0.010\)) were significantly higher within the GM group.

Avoiding the need for multiple stents (and hence the risk of failure to overlap) by maximising the length of the individual stents used may assist in the avoidance of GM. The Xience Prime and the TAXUS Liberte Long stents may therefore offer an advantage over other DES. The XTENT Custom NX DES should carry little risk of GM due to failure to overlap, unless lesion length exceeds 60mm. GM due to failure to overlap or to fully cover the diseased or injured vessel may also be reduced if stent radio-opacity is optimal, facilitating accurate stent positioning. While reduction in stent strut thickness enhances deliverability and may reduce the risk of side-branch occlusion, it also potentially reduces radio-opacity. Novel alloys such as the platinum–chromium alloy of the next-generation TAXUS Element and Promus Element DES (Boston Scientific) aim to preserve radio-opacity while minimising strut thickness, and may help to overcome this problem.

Stent Thrombosis

Although still rare, very late ST appears to be more common with DES than with BMS. Registry data have found stent length to be an independent predictor of very late ST.\textsuperscript{47} However, while minimising the risk of very late ST is clearly an important goal, it would appear unlikely to be a key factor determining the choice of DES in the specific treatment of long lesions.

It has also been suggested that the cumulative effect of ‘double-dose’ metal, polymer and drug resulting from stent overlap (common in long lesions) may increase the risk of acute and subacute ST.\textsuperscript{48} However, this was not confirmed on late follow-up (to 1,080 days) from the collective experience of four randomised comparative trials of SES versus BMS, which found no evidence of an increase in early stent thrombosis.\textsuperscript{49}
Conclusions
The superiority of DES over BMS in the treatment of long lesions is unequivocal, and their use will remain routine in this clinical setting. However, the increasing treatment of more diffuse coronary disease poses specific challenges for DES. The ideal DES for long lesions would offer low late loss to minimise the risk of restenosis. Thin struts should be employed to reduce the risk of side-branch occlusion and hence peri-procedural infarction, as well as to enhance deliverability. However, radiation of opacity despite minimisation of strut thickness is also important to aid stent positioning and avoid GM. The availability of very long stent lengths to circumvent the problems of stent overlap (including failure to achieve overlap) is desirable. However, maintenance of deliverability even with extra-long devices by optimal design of the delivery catheter, balloon and stent/polymer complex will be essential. Of the currently available DES supported by robust randomised controlled trial data, it is clear that some satisfy these criteria for the ideal long lesion stent more than others. What is also certain is that the practising interventional cardiologist will increasingly be called upon to treat long lesions, and will need to understand the challenges faced and the merits of the various available DES technologies. Clearly, different stents perform differently in long lesions and therefore it is important that a decision on which to use is made based on the most compelling clinical data.

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