

A Brief History of Drug-Eluting Stents

This article reviews the evolution of drug-eluting stents (DES), assesses the current market situation and predicts how it might develop in the foreseeable future.

Coronary angioplasty - also known as percutaneous transluminal coronary angioplasty (PTCA) – was first introduced in the late 1970s as a minimally-invasive means of re-opening coronary arteries that had become narrowed with plaque, so restricting blood flow. The procedure involves a balloon being inserted via a catheter into a peripheral artery and guided to the blocked coronary artery, where it is inflated to compress the plaque against the artery wall to re-establish blood flow, before being removed.

However, it soon became apparent that balloon angioplasty had its limitations: in a relatively small number of cases the process weakens the artery wall to such an extent that although it is successfully dilated, it collapses once the balloon is deflated ('elastic recoil'), leading to the need for emergency bypass graft surgery (CABG). But a much greater problem is restenosis - the phenomenon whereby the artery begins to renarrow as a result of the body's healing response to the trauma of angioplasty: the equivalent of scar tissue forming over an injury. This has been observed in between 30 and 40 percent of all procedures within the first year.¹

Bare-metal stents (BMS) were introduced in the mid-1990s with the aim of overcoming the deficiencies of balloon angioplasty. Essentially expandable mesh cylinders, they are mounted on a balloon and open out once inside the coronary artery to line the wall. Subsequent refinement to earlier designs offer improved flexibility, making it easier to deliver to the narrowed artery. Yet although BMS certainly overcame the problems of artery wall collapse by propping it open once the balloon is deflated, the challenge of restenosis was found to persist, although not to the same degree as with balloon angioplasty: in between 20 and 30 percent of cases the treated artery was found to re-narrow within six months of stent insertion, leading to the need for a repeat procedure.²

Insertion of a BMS can cause an additional problem: although the stent is eventually incorporated into the artery wall as tissue forms over it ('endothelialization'), beforehand there is a risk that the blood clots due to the presence of a 'foreign body', forming a potentially life-threatening blockage (thrombus) to the artery. For this reason, patients given a BMS are advised to take a combination of anti-clotting drugs for at least three to six months after initial insertion.

Drug-eluting stents (DES) were developed to specifically address the problems of restenosis encountered with BMS. They consist of a BMS coated with a polymer which gradually releases a drug to inhibit the cell proliferation that causes restenosis. By the time all the drug has been released by the polymer - a period of between six and nine months – the main risk of restenosis has been minimized.

The first DES to be launched was the Cypher[®] stent in 2003, followed by the Taxus[®] stent in 2004. Others followed over the ensuing years. Apart from physical differences in the design of the stent itself (type of metal used; strut thickness; mechanics of strut interlinkage) the differences between the variety of DES currently available relate to the actual antirestenotic drug used and the release characteristics of the polymer (how much drug is released and how rapidly this occurs).



There is a steadily-increasing body of clinical data comparing individual DES both with their BMS equivalents and with each other. It is evident that DES significantly reduce the incidence of restenosis compared with BMS, to levels of under 10 percent.³ The clinical benefits of one DES over another are less clear-cut, although a number of studies have shown that the so-called 'second generation' DES are superior to 'original' DES in terms of preventing further cardiovascular complications or the need for a repeat stenting procedure, as with Xience[®] versus Cypher.⁴

However, by the late 2000's a problem started to emerge with DES which hadn't been seen with BMS: that of very late stent thrombosis.² This is the phenomenon of a thrombus developing inside the stent more than a year after insertion: far later than usually observed with a BMS. No-one is yet certain what causes this, but there are two main potential culprits: the antirestenotic drug which can delay endothelialization; and hypersensitivity reactions to the polymer, which remains coating the stent once it has released all of its drug. For this reason patients are currently advised to take anti-clotting drugs for at least a year after they receive a DES - longer than with a BMS.

This led to renewed debate as to whether a DES really was potentially superior to a BMS in terms of saving lives: does the benefit of reduced restenosis outweigh the drawback of late stent thrombosis, and the associated need for a longer course of anti-clotting drugs? Analyses of all the currently-available data suggest that on balance it does, although it is difficult to demonstrate a clear cost-effectiveness argument for a DES over a BMS, which has led to their use being restricted by healthcare providers⁵.

The latest developments in DES technology are therefore understandably focusing on how to overcome the problem of late stent thrombosis, while retaining a superior clinical profile. Leading the field is the development of stents with biodegradable polymers, where the polymer breaks down once it has finished releasing the drug, essentially leaving a BMS.

A number of companies have stents with biodegradable polymers under development, but to date there are only two widely available: BioMatrix[™], launched in 2008; and Nobori, which uses the same polymer and drug under licence. The naturally-occurring polymer fully degrades from the stent after six to nine months, as it releases Biolimus A9[™]. This drug has been specifically designed for use in drug-eluting stent systems and has the highest lipophilic profile of the common limus drugs, enabling rapid absorption by the tissue and minimizing systemic exposure.

The latest version of BioMatrix, the BioMatrix Flex[™], launched in 2010, features a more flexible stent platform for improved deliverability.

The most recent three-year data shows a strong trend towards a significantly lower rate of MACE (Major Adverse Cardiac Events) in patients treated with BioMatrix Flex versus those treated with Cypher[®] Select[™], in an "all comers" patient population.⁶ Occurrence of late stent thrombosis was very low: a cumulative 0.2 percent over the three year period.⁶

Other notable current developments in stent technology are polymer-free stents where the drug is released directly from the stent, and completely bioresorbable stents where the stent platform, along with its polymer coating, degrades over time. However, neither of these stent developments is yet commercially available, and their long-term safety and efficacy have yet to be proven in a sufficiently broad range of patient types.

References

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