Chapter

163

Next Generation Drug Eluting Stents

ATUL MATHUR, SANJEEV SHARMA

With several drug eluting stents (DES) already available and several others in pivotal clinical trials, interventional cardiologists are starting to hope that innovations will resolve many of their concerns with existing products. With any breakthrough technology that changes landscape of medical therapeutics, the reality is, the first version is always the worst version.

IMPROVING DELIVERABILITY

While second-generation products, Cypher Select and Taxus Liberté, are already CE Mark and FDA approved, both have focused primarily on enhanced deliverability over their first-generation versions. Majority lesions are simple lesions where deliverability of first and second generation devices is not an issue. However, it is the complex anatomies where these devices fail more often. With advent of drug eluting stents, its main benefit lay in tackling complex lesions, often which were referred to Bypass Surgery early on. This is where the Third-generation devices have made rapid improvements with innovation in stent composition and design. Many new generation drug eluting stents available outside North America have done away with stainless steel for the stent platform, replacing it with alloys that maintain radiopacity and strength but permit thinner, more flexible struts. In order to improve deliverability, newer devices use new materials like Cobalt Chromium (Xience V, Abbott), Cobalt Nickel (Endeavor, Medtronic) and Cobalt Alloy (Co-star), etc. These allow significant reduction in strut thickness and improvement in stent flexibility.

DRUG RELEASE

Elsewhere, companies have tried to emulate or improve on the success of Cypher by developing new macrolide immunosuppressive ("limus") drugs, such as Biolimus A9 (Biosensors), Everolimus (Abbott), Tacrolimus (Sorin, Abbott), and Zotarolimus (Abbott, Medtronic) for stent-based delivery (Fig. 1). In the newer stents, limus family drugs seem to be the drug of choice, while paclitaxel seems to be losing on its early popularity. Companies are even trying to coat stents with multiple drugs that address multiple restenosis pathways. However the debate doesn't end with drug selection. Other parameters that companies are looking to improve upon are drug concentration and drug release. It is a constant endeavor to reduce drug concentration without compromising efficacy. There is also an effort to achieve drug release kinetics that mimics restenosis cascade, which is known to occur till 120 days post-stent implantation. Some earlier products, like Taxus elute only 15-20% of its drug and that too in first few days, while Endeavor elutes almost 100% of its drug in the first 15 days. Cypher from the early generation devices comes close as it elutes drug over 90 days post-implantation. This understanding has led to further improvements, with Abbott's Xience V eluting Everolimus over 120 days, covering entire restenosis cascade and Medtronic changing its polymer in its next generation stent to get similar release profile.

PUZZLING OVER POLYMERS

Perhaps most contentious flurry of activity centers on the actual mechanics of drug-delivery. Polymers have been hailed by some as essential to controlled drug elution and maligned by others as a ticking time bomb: the potential cause of increased late thrombosis and other adverse tissue responses. The polymer has also been blamed for stent-delivery glitches; in particular, increased friction, or "stickiness," between the delivery

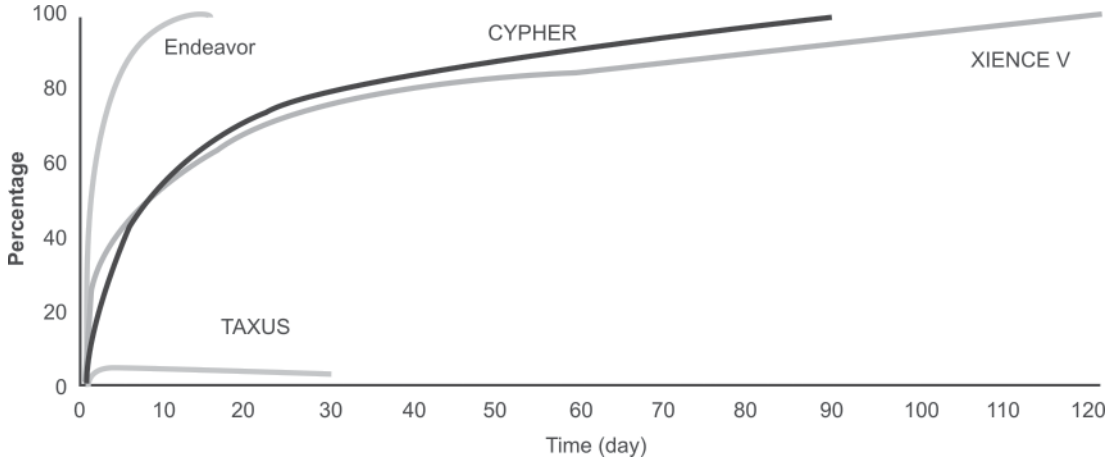

Fig. 1: Controlled release pattern across DES

Source: Medtronic Vascular Data Presentation, TCTMD; Taxus IV SR Presentation, TCTMD; Cypher Presentation, TCTMD *(Data on File at Abbott Vascular)*

balloon and the stent itself. Although the original Taxus and Cypher stents both have polymer coatings, other DES developed at the same time, such Cook Inc's drug eluting stent program, did not make it through clinical testing, having failed to demonstrate superiority over bare-metal stents—a fault blamed largely on the inability to regulate elution of the drug.

New stents, however, are revisiting the concept of polymer-free drug delivery or using polymers that disappear over time. Long-term outcome of bare stents is well known, whereas that of polymer coatings is not. Even a polymer that is not loaded with drug can cause localized reactions in the artery. Scanning electron microscope studies also indicate that polymer integrity can also be damaged during stent delivery, paving way for an inflammatory reaction.

Animal data form the latest generation cobalt chromium drug eluting stents such as Xience V (Abbott) and Endeavor (Medtronic) suggests that they induce less inflammation and have rapid endothelialization in pig and rabbit models and will likely be safer in man. Moreover, long-term safety of a DES depends on the extent of rapid re-endothelialization, functional endothelial layer, no long-term inflammation associated with the implant as well as the resolution of fibrin.

Other companies are working to get around the problem of polymer tackiness and tissue reactions by using them only on the abluminal surface of the stent. The idea is to direct drug at the vessel wall, and not the bloodstream; indeed, even Biosensor's non-polymerized paclitaxel-coated Axxion stent is coated with drug on its outer (abluminal) side only. Likewise, the Janus stent's reservoir design releases drug only on the outer aspect of the stent. These newer generation DES are summarized in Table 1.

NOW YOU NEED IT, NOW YOU DON'T

The distant future calls for drug eluting stents that not only has biodegradable polymers but biodegradable platforms as well! Such devices best described as

Table 1: Currently available newer generation DES

Manufacturer	*Name*	*Drug*	*Stent material*	*Polymer*	*Status*
Abbott	Xience V	Everolimus	Cobalt chromium	Durable	CE Mark
Biosensors	BioMatrix	Biolimus-A9	Stainless steel	Bioabsorbable	—
Conor	CoStar	Paclitaxel	Cobalt chromium	Bioabsorbable	CE Mark
Cordis/J and J	Cypher Select +	Sirolimus	Stainless steel	Durable	CE Mark
Medtronic	Endeavor	Zotarolimus	Cobalt chromium	Durable	CE Mark
Sorin	Janus	Tacrolimus	Stainless steel	None	CE Mark
SMT	Infinnium	Paclitaxel	Stainless steel	Bioabsorbable	CE Mark
Terumo	Nobori	Biolimus-A9	Stainless steel	Bioabsorbable	—

"fourth-generation" devices, namely fully bioresorbable stents are made completely out of dissolving polymers or magnesium. Companies like Reva, Endovasc/ TissueGen, and Igaki-Tamai have all presented or published data in recent years on stents made completely out of biodegradable polymers that elute drug as they dissolve. Taking another tactic, Biotronik is working away on a drug eluting magnesium-based alloy that degrades over the course of approximately two months and, in 2004, signed an agreement with Conor to develop a fully absorbable magnesium-based DES. Abbott's ABSORB FIM clinical trial is underway in New Zealand and Europe and according to Dr. John Ormiston (PI for Absorb Study), fully bioabsorbable everolimus eluting stent may be the future for PCI's. The trial has so far enrolled 30 patients and the data presented at TCT 2006 revealed 0% MACE and 0% SAT at 30 days.

Even though many a products exist in the market today, the next-generation is trying to address various shortcomings. The therapy is going through rapid development and future looks bright for all our patients.