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Therapeutic focus – Bioresorbable stents are here to stay

Elizabeth Cairns

Dissolving stents – scaffolds that treat coronary artery disease by propping the vessels open before breaking down in the body and vanishing – are starting to have a marked effect on the interventional cardiology sector. The first such device, Abbott's Absorb, has been on sale in Europe for 18 months and will soon be joined by a second very similar scaffold, Elixir Medical's DESolve (*EP Vantage interview – CE mark for dissolving stent pits Elixir against Abbott, June 10, 2013*).

But already other small companies are developing rival scaffolds using different materials, pushing innovation as a way to compete with the much larger Abbott, and by the end of next year two more devices could be on the market. More importantly, it is possible that these new technologies could become workhorse products, taking share from permanent DESs in the same way that DESs displaced bare-metal stents.

Now you see it

The devices treat the same disorder as DESs and bare-metal stents: coronary artery disease, the single most common cause of death worldwide. Atherosclerotic plaque builds up inside the coronary arteries, impeding blood flow to the heart. Stents are tiny mesh tubes implanted percutaneously to prop the artery open.

The trouble with permanent metal stents, drug-coated ones particularly, is that they increase the risk of thrombus formation, necessitating long-term medication with blood thinners such as Plavix and Aspirin. Scaffolds that reopen narrowed arteries but do not outstay their welcome also necessitate this drug therapy but for a much shorter duration.

Furthermore, the temporary devices allow the artery to return to its de novo state, restoring its contractility and allowing pulsatile vasomotion and less turbulent blood flow.

The material used to make the scaffolds has a profound effect on how quickly they break down. Abbott and Elixir have both plumped for polylactide, a type of polyester also used to make dissolving sutures. The formulations are slightly different; Elixir's DESolve does exactly that within a year of implantation, whereas Absorb takes around twice as long.

Now you don't

The two other companies with bioresorbable scaffolds in late-stage development are a little more adventurous in their choice of materials (see table). California's Reva Medical uses a polymer based on the amino acid tyrosine called desamino-tyrosine polycarbonate.

Reva's chief executive, Robert Stockman, told *EP Vantage* that this substance was very strong, and its strength and therefore its durability could be varied. "We can adjust the amount of time it maintains its strength before it goes away. In our case we maintain the strength of the polymer for six months; that's long enough for the scaffold to do its job."

Mr Stockman points out that it will take a while for dissolving scaffolds to become established. "The challenge for these new devices is to prove over many clinical trials and many thousands of patients that they live up to their promise, and that is happening right before our eyes."

Absorb has done reasonably well since its approval in late 2011. "There's a very strong conversion over to that product now," Mr Stockman says. "Abbott has shown such strong clinical progress with the device."

He says that Reva's bioresorbable scaffold, called ReZolve2, ought to gain CE mark and launch in Europe next year. "That suits us just fine because the advantages of our product will be seen once we get into the market, and much of the conversion to this new technology will have taken place, and will set us up, we hope, for good commercial success."

One intriguing angle to Reva's device is that, through the addition of iodine to the polymer, it can be rendered visible under X-ray. Mr Stockman explains that Absorb and DESolv are invisible, "except that they have little

markers – gold dots at the ends of the scaffold – so at least you can see the front and back end, but you can't tell if the device is broken or if it fits tightly against the wall of the artery". Additionally ReZolve2 does not require refrigeration as the two polylactide scaffolds do.

Loss

The other company with a scaffold in late-stage trials, Biotronik, has taken a different tack entirely. Eschewing polymer, the German company has chosen to use a magnesium alloy as the basis for its structure, known as the drug-eluting absorbable metal scaffold or DREAMS.

Magnesium is one of two possible choices of a bioresorbable metal, the other being iron. The compound eluted by DREAMS is also an outlier; rather than choosing a limus drug Biotronik opted for paclitaxel.

Drug-eluting bioresorbable scaffolds						
Company	**Product**	**Scaffold material**	**Drug**	**In-scaffold late lumen loss at 6mth (mm)**	**In-scaffold late lumen loss at 12mth (mm)**	**CE mark**
Abbott	Absorb	Polylactic acid	Everolimus	0.19	0.27	January 2011
Elixir Medical	DESolve	Polylactic acid	Novolimus	0.21	–	May 2013
REVA Medical	ReZolve2	Desamino-tyrosine polycarbonate	Sirolimus	–	0.20	Expected 2014
Biotronik	DREAMS	Magnesium alloy	Paclitaxel	0.68	0.52	Expected 2014

The three polymer-based devices have shown similar clinical performance. Their most important metric is in-scaffold late lumen loss – the difference between the diameter of a stented vessel post-procedure compared with the follow-up angiogram at six or 12 months. This shows how well the scaffold has held the blood vessel open.

It is here that Biotronik's candidate has come unstuck. Its late lumen loss at 12 months was 0.52mm, a disappointing finding compared with the 0.27mm seen with Absorb. Permanent DESs have historically exhibited 12-month late loss values in the range of 0.20mm to 0.40mm, which has generally corresponded to positive long-term outcomes.

Biotronik said that paclitaxel might not have been the ideal choice for its scaffold. It is considering trialling a new limus-based formulation, but says that it can still obtain CE mark for the paclitaxel version of DREAMS by the end of 2014.

Dissolving coronary scaffolds are making inroads in Europe, with Abbott's Absorb, the only one actively marketed so far, occupying around 5-10% of the drug-eluting stent market. This is despite a significant price premium; Absorb is believed to have reimbursement approval in Germany at €2,750 or approximately $3,600 – three and a half to four times as much as the average permanent DES.

The US is another matter. The FDA's requirements for approval are generally more stringent than those of the various European authorities and this market is true to form.

Abbott has begun its pivotal US trial but this will not read out until 2015. Elixir plans to apply to the FDA for permission to begin its pivotal study in 2014, and Reva will follow. For this type of technology to become widely accepted it must make its way to the US.

Dissolving stents could come to be used alongside permanent DESs and might even come to replace them in many cases. But this will take time; scaffold developers must persist in their efforts to bring the devices to market, even if the devices themselves do not persist at all.

To contact the writer of this story email Elizabeth Cairns in London at elizabethc@epvantage.com or follow @LizEPVantage on Twitter