INTERVIEW

Next generation drug-eluting stent technology: the polymer-free era has begun

Stenting efficacy has improved with the use of stents that release antiproliferative drugs. Traditionally, the drug has been released from a polymer coating; however, this coating can be associated with inflammation. Confluence discussed the concept of polymer-free drug-filled stents and the ongoing trial of such a stent with Professor Stephen Worthley, Helpman Chair of Cardiovascular Medicine at the University of Adelaide.

Could you start by explaining what a drug-filled stent is?

Stephen Worthley (SW): To give some background, the current standard of care for treating patients with severe coronary lesions are so-called drug-eluting stents (DES) and there are a number of these available. They are basically metallic, thin strut stents that have a medication on the stent that reduces the risk of restenosis. The anti-proliferative medication is embedded in a polymer, or plastic coat, that surrounds the stent, such that it is slowly released over a period of 3–4 months – this is important because that is the time frame during which restenosis can occur. The polymer is important because if you dipped the metallic stent in a medication, it just completely dissolves or elutes off the stent immediately. The polymers allow the medication to elute over several months, helping to stop the re-narrowing.

The problem with polymers is that when the medication has gone, they remain in the vessel and can induce inflammation in the vessel wall. It is this inflammation that delays the healing of the vessel at the stent site. DES have been a great step forward in terms of efficacy of stenting, meaning they reduce the risk of re-narrowing of the vessel, but at the same time they delay the healing, and this has led to concerns around stent thrombosis. Some novel therapies use what are called ‘bioreabsorbable polymers’, which means that the polymer itself can dissolve away over a period of time. However, even they run the risk that in the process of dissolving they may induce inflammation, and so delay healing.
The perfect scenario would be if we could find a way to slowly release a medication, a little like drip-feeding, if you like, without using a polymer or coating. In theory you have then achieved the Holy Grail where you could still have slow release of medication, thereby stopping the re-narrowing process, and by avoiding use of any polymer the vessel could heal rapidly so you have a lower risk of clot formation. That is the premise of the drug-filled stent – it used exactly that concept; finding a way to slowly release the medication and yet have no polymer.

This was achieved using a reservoir of medication that is held within the stent scaffold itself, which contains abluminal laser-drilled holes, 20 microns in diameter, that allow elution of the anti-proliferative medication (sirolimus [Rapamune®, Pfizer, New York, NY, USA] in this example). Prolonged drug release is achieved through this unique technique of microscopic holes, meaning that there is no polymer (figure 1). The early pre-clinical work confirmed what we thought we would see, which is that there is prevention of re-narrowing and yet an early healing process.

Is there anything else that is different about the structure or anything else that is important?

SW: Yes, it is an amazing feat of biomedical engineering. The stent is fashioned to leverage Medtronic’s Continuous Sinusoid Technology, which is in the Integrity® stent (Medtronic, Minneapolis, MN, USA). What that means is that, rather than making the stent from a solid tube and then laser-cutting components out of it, which is how the traditional stents are formed, this stent uses a single extruded wire fashioned into a sinusoidal pattern, and the stent structure is formed of repeating circular elements of this sinusoidal extruded wire (figure 2A). This allows the drug-filled stent to make use of a tri-layered wire (figure 2B). There is an outer cobalt chromium component, the middle layer is a very thin layer of tantalum, which is very radiopaque and allows us to see the stent more clearly on x-ray, and an inner sacrificial layer that is removed, forming a continuous inner lumen that is coated with the drug. Then, the 20 micron holes are laser-drilled through the outer layer of the stent that faces the vessel wall, to enable delivery of the drug into the tissue.

There is also another element to it. The strut itself is said to be swaged, which means that the circular wire is flattened to form an oval, giving a very narrow strut, approximately 80 microns thick. This means that the distance the cells have to grow from the vessel wall over the top of the strut is less. This property utilises data that we have had for a long time, which shows that in the bare-metal stent, the thinner the strut was, the lower the restenosis rate. We do have evidence from bare-metal stents that thinner struts are associated with a more efficacious stent (even in the absence of anti-proliferative medication).¹

What would improve healing and lower inflammation mean in a clinical setting for the patient?

SW: That is a good question, and what it means, in theory, is that if we had a stent that was as effective at reducing restenosis as a DES and yet healed more rapidly, there is the potential to get patients off the aggressive blood thinning therapies that we use currently, sooner. For example, in the USA, the FDA mandates that with the current DES, patients should be on dual antiplatelet therapy for 12 months — usually aspirin and clopidogrel,
Study design for the RevElution trial (A) and detail regarding the OCT imaging cohort (B).

Figure originally presented at TCT 2015, San Francisco, CA, USA.
but it can be any other products like aspirin and ticagrelor (Brillique®, AstraZeneca, London, UK) or aspirin and prasugrel (Efient®, Eli Lilly, Indianapolis, IN, USA) – although we do have reasonable safety data for 6 months of therapy. Many of the patients that we treat now are elderly, and they may have high bleeding risk or may need early surgery after a stent implant, so potentially being able to interrupt antiplatelet therapy at a much earlier time point, for example after 1 month, is very attractive. With a stent that, in theory, heals more rapidly you could minimise the patient’s exposure to prolonged blood thinning therapy.

Could you tell us about the RevElution trial?

SW: We started the RevElution trial in July 2015 in Australia. It has a slightly complicated design. It is a 100-patient study that is basically divided into two cohorts of 50. The primary endpoint for the first 50-patient cohort is late lumen loss at 9 months, which is basically the amount of re-narrowing inside the stent. In the second 50-patient cohort, the primary endpoint is late lumen loss at 24 months (figure 3A).

Furthermore, to gain some insight into the concept of early healing, we have embedded a number of sub-studies within these two 50-patient cohorts, using a high resolution intravascular imaging technology called optical coherence tomography (OCT; figure 3B). This is an intravascular probe that is placed inside the coronary artery at the time of an angiogram procedure, which gives very high resolution imaging of the tissue as it heals around the stent struts, providing an indication of healing within the coronary arteries.

Within each of the two major 50-patient cohorts, we have two 15-patient cohorts, so a total of 30 patients, that will get OCT. The two 15-patient cohorts from the 9-month primary endpoint group will have OCT at 1 month and 3 months, as well as the primary endpoint at 9 months. The remaining 20 patients in this group won’t have any imaging at 1 or 3 months, only at 9 months.

In the 24-month primary endpoint group, one subset of 15 patients will have OCT imaging at 2 months, and another, separate 15 will have imaging at 6 months, both in addition to the primary endpoint at 24 months. Likewise, there will be 20 remaining patients who will just have the imaging at 24 months.

What that allows us to do in a slightly complicated design, is gain information from OCT across this 100-patient cohort at 1, 2, 3, 6, 9 and 24 months. Although of course they are not all paired datasets, it is information that we will be able to gain around this healing and efficacy story. It is a very rich dataset from just 100 patients that will enable us to work out if the early healing signal is real, and if it is real, then we can design an appropriately powered clinical trial to answer the question of whether 1 month of dual antiplatelet therapy is enough.

Are there any interim data available from RevElution?

SW: We presented some of our early data in October 2015 at the Transcatheter Cardiovascular Therapeutics (TCT) meeting in San Francisco. We saw exactly what we had hoped to see in terms of early OCT imaging. In those patients who had the drug-filled stent implanted, there was early healing and early coverage of the struts. At 1 month, 90% of the struts were covered or had a healing process, yet there was no severe proliferative healing seen in those early patients. To date we have treated 41 patients out of this 100-patient study, and over the next 12–24 months we will gather more information around the healing process and the efficacy of the drug-filled stent platform out to 12 and 24 months.

How does this stent compare to other polymer-free stents?

SW: There really is only one other polymer-free drug-coated stent that is under investigation at the moment; the BioFreedom™ stent (Biosensors International Ltd., Singapore). BioFreedom™ was recently studied in a trial looking at the safety of this stent versus bare-metal stents in patients who needed to come off blood thinning therapy at an early time frame of 1 month. The results were presented at TCT this year. Interestingly, the BioFreedom™ stent is simply a bare metal stent with a micro-structured, or scratched, abluminal surface that increases surface area. That surface is coated with an antiproliferative medication, BA9, which seems to remain in some of the crevices and nooks on the scratched out surface and is released over time. One important distinction between the BioFreedom™ platform and the polymer-free stent is that the majority of the drug is eluted from the scratched surface within the first 30 days, compared
with a delayed elution over 90 days for the polymer-free stent. Although the BioFreedom™ stent was superior to a bare metal stent in terms of efficacy, this shorter elution period does raise a question about its efficacy in preventing restenosis versus current generation DES, especially in more complex patient groups.

Are similar trials being done with stent and polymers over more traditional drug-eluting stents?

SW: Yes, there have been, but we don’t have any at 1 month though. We have seen, for example, that there was a small study with the XIENCE stent (Abbott Vascular, Santa Clara, CA, USA) looking at strut coverage at 3 months, and in that study it was about 70%.

To be fair, there is some variation in how we define strut coverage. It is such a new technique, and if you like we are forging the field ahead in terms of using this technique to assess the efficacy of the stent, so it is hard to compare studies. Having said that, it is very exciting that in this early patient group we are seeing 90% strut coverage at 1 month – that is far better than we thought we would see.

Thinking about some of the patients in the RevElution trial, what are the characteristics of their lesions?

SW: They are typical first-in-human type patients. On the whole, the lesions are fairly simple and straightforward. Patients need to have ischaemic-induced problems, so haemodynamically significant coronary artery lesions in a coronary vessel between 2.25 and 3.5 mm in diameter. The lesion length must be less than 27 mm without excessive calcification or tortuous coronaries. The lesion cannot be in a left main artery, it cannot be a chronic total occlusion and there cannot be bifurcation of the lesions. Patients do need to be able to tolerate dual antiplatelet therapy with aspirin and clopidogrel for at least 6 months and, as part of the trial, consent to the follow-up imaging that is an intrinsic part of the protocol. These patients are reasonably reflective of the patients that we would see in the cath lab with stable coronary disease, although as coronary intervention has become more complex we have extended it to chronic total occlusion intervention and acute infarct angioplasty, and these two patient subsets would be excluded from the study.

Do you see this technology being able to expand to and become suitable for use in these more challenging type of patients?

SW: Absolutely, and in fact, they are the exact patient group who potentially may experience the greatest benefits from this therapy. Drug-filled stents may show the greatest clinical utility in more complicated lesions where healing may be impeded, or for example, where there may be an issue when you have overlapping stents.

In the RevElution trial, there has been one patient so far at the 1-month time point that had overlapping stents. Sometimes when we put a stent in a patient there might be an extra section or injury, and then we will place another stent overlapping the first stent. What has worried us in the past is that if you have two stents, then the distance for the healing to occur over is twice as far, potentially requiring twice the concentration of medication. The OCT images in that one patient showed beautiful healing over the overlapping stent; however, this example gives us a sample size of only one, so we are cautious about making too many overarching statements based on this. Clearly this dataset will empower us to do a future all-comers type of study, where chronic total occlusions or infarct percutaneous coronary intervention and bifurcations are included to confirm whether the safety and efficacy signal is translated into all-comer patients.

In terms of the data presented at TCT, are there any other key standout findings that we should be talking about?

SW: The strut coverage, for me, was probably the most striking thing. Ninety percent strut coverage at 1 month was definitely better than we had thought we would achieve, bearing in mind that there is not a lot of benchmarking available in that early timeframe. We will look to populate the image dataset over the next 6 months with the other patient timepoints.

In terms of efficacy, the neointimal hyperplasia area was 0.5 mm² and the neointimal diameter loss was 0.06 mm. One month is an early timepoint to be getting too excited about efficacy, but all of the results are commensurate with what we would expect to see. Although there is healing over the stent strut, it is thin, and consistent with the fact that there has been suppression of excessive neointimal proliferation.
Are there any other benefits or challenges associated with the technology?

SW: The polymeric stents that we use now, which are a plastic, are a little bit sticky or adhesive, so the fact that we have a non-polymeric drug eluting platform means the stents are easier to deliver. They are smoother, if you like, as you track them through the coronary artery, so there is a little extra benefit in terms of deliverability from a technical perspective for the interventionalist.

The challenges that we face, simply, are discovering whether there is a downside. Conceptually there is not, and at the moment we are in the midst of making sure that we do a good job of the clinical trials to ensure that we get good, robust data from which we can accurately identify what the signals are.

The one comparator to add might be, for example, that there has been a lot of excitement in the coronary intervention space about bioresorbable stents. This is the concept of a stent that you could implant that would dissolve away over time, and in 2 or 3 years’ time there would be no scaffold left behind at all, so the coronary artery goes back to its normal biology.

The drug-filled stent is a metallic stent that will stay in situ, but a lot of data have come out in the last few months from the most studied bioresorbable scaffold – the Absorb stent (Abbott Vascular). In the Absorb trials, ABSORB II and ABSORB III, the issue has been that the stents have very thick struts of 160 microns; this is twice the thickness of the struts in the drug-filled stent. The bioresorbable stents are not very compliant and don’t have very high radial force so if you try to embed them and over-expand them, they can unravel and rip. They are basically a plastic, made of poly-L-lactic acid (PLLA).

What we have seen with the ABSORB II and the ABSORB III studies is that, in the first 12 months there is a higher stent thrombosis rate in the patients who receive the bioresorbable stent versus the current-generation DES. This is because, although these stents dissolve, they do still induce inflammation, and they are very thick strut struts. So we have not seen the bioresorbable stents stand up to the current-generation DES with regard to that endpoint. At the moment, this polymer-free drug-filled stent technology looks like it could be the future of current intervention, until such time as we can get that bioresorbable scaffold improved. Currently we do not have the technology to be able to make a bioresorbable scaffold that would induce no inflammation and have the same healing capacity that we see with something like the polymer-free stent.

Is there anything else you think we need to know?

SW: Just that it is early days. It is an important caveat to note that we are at the start of the journey with the drug-filled stent, so whilst we are seeing a lot of excitement, we do need to watch this space to see how things go in the longer term. The early signals are exciting, but clearly the completion of the trials and the presentation of the data will be important. To date we have 41 patients treated, and we have not seen anything yet that has raised a concern, and all the early signals have been as promising, if not more promising, than we thought they might be. All 50 patients were enrolled by the end of 2015, so that will mean that for the 9-month primary endpoint cohort, we should see late breaking data at TCT next year in the US. We are presenting the 3-month OCT data at the American College of Cardiology meeting in Chicago in 2016, so there will be some data coming through the year that will add to the story, but watch TCT next year for the primary endpoint.