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A novel drug-filled stent: 9-month results from the RevElution trial

Stent technology is continually advancing from the use of durable polymers to the development of bioabsorbable and polymer-free devices, which may carry a reduced risk of thrombogenic side effects. *Confluence* spoke with co-principal investigators of the RevElution trial, Dr Alexandre Abizaid of the Institute Dante Pazzanese of Cardiology, Sao Paulo, Brazil, and Professor Stephen Worthley of the Royal Adelaide Hospital and St Andrew's Hospital, Australia, to discuss the results of their investigation into the safety and efficacy of a novel drug-filled stent for the treatment of coronary lesions.

The RevElution trial made use a novel drug-filled stent (DFS). What makes the design of this device so unique?

Dr Alexandre Abizaid (AA): The DFS used in the RevElution trial uses the same design as a best-in-class drug-eluting stent (DES), such as Resolute Integrity™ and Resolute Onyx™ (Medtronic). Although they share the same structure, the material and drug delivery used differs. The DFS has an outer cobalt chromium layer, a middle tantalum layer, and an inner lumen coated with sirolimus. The combination of metals used in the design provides good strut strength and radiopacity. Small, laser-drilled holes on the abluminal stent surface control drug elution, releasing sirolimus into the vessel wall through natural diffusion and removing the need for a polymer (Figure 1). Acute performance is effective due to the delivery system, and the design of the stent offers a good platform for drug delivery, as well the ability to navigate to difficult, calcified regions of the anatomy. Most of the Medtronic platforms have these characteristics.

Professor Stephen Worthley (SW): The DFS behaves like a thin strut stent in terms of deliverability. It is a very deliverable stent and could be not only a 'workhorse' stent, but in fact a stent you could use to get to quite difficult positions. There are some concerns around using the current bioabsorbable polymers for the smaller calibre vessels (2.25 mm) and there are also issues around whether to use intravascular imaging to ensure that you have proper stent apposition with the vessel wall without oversizing it.

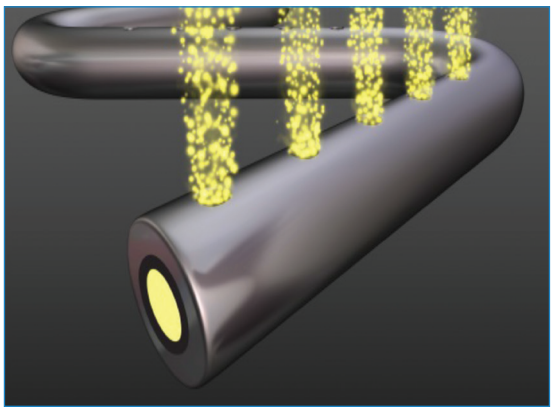


fig. 1

Elution through abluminal holes in the drug-filled stent is controlled through natural diffusion via direct interaction with the vessel wall.

As a clinical 'workhorse', therefore, the DFS stent is clearly an excellent candidate.

What advantages does having no polymer offer?

AA: Polymers have the potential to become thrombogenic. Thick, durable and permanent polymers were the cause of some of the thromboses observed with first-generation devices. There were advances in stenting technology with the development of bioabsorbable polymers that disappeared within 9 months. With newer devices, such as SYNERGY™ from Boston Scientific, it can now take only 3 months for the polymer to re-absorb. However, removing the polymer altogether could enhance safety even further, as you have one less thrombogenic factor to provoke stent thrombosis.

How is a DFS different from a durable polymer stent and bioabsorbable stents?

SW: The efficacy that we gain with a current-generation DES is due to a release of anti-proliferative drug that is sustained over a

fig. 2

Late lumen loss cumulative frequency distribution at 9 months. The primary endpoint was met, demonstrating non-inferiority.

3–4 month period, bar the presence of a polymer. The polymers, which are crucial for giving that controlled, sustained release of anti-proliferative drug, can either be permanent or bioabsorbable. In pre-clinical trials, some polymers have been shown to be associated with some inflammatory cellular infiltrate. It is this inflammatory cellular infiltrate that delays endothelialisation and the healing process. The DFS might be more favourable from an efficacy perspective because the polymer-free technology allows the controlled, sustained elution of an anti-proliferative agent over 90–120 days without the presence of the polymer and thus no inflammatory reaction.

What was the rationale behind the RevElution trial?

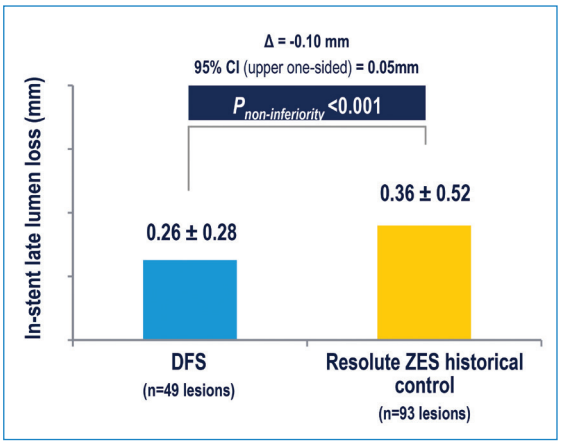
SW: The current generation of DES have shown very good suppression of neointimal hyperplasia in the treatment of patients with coronary lesions. However, we know that late stent thrombosis and delayed healing can occur when DES are used. Additionally, some patients require cessation of dual antiplatelet therapy (DAPT) due to unforeseen, urgent surgery, for example. If this happens early, it can be accompanied by a risk of stent thrombosis, which carries significant morbidity and mortality risk.

The RevElution trial investigated the safety and efficacy of the unique polymer-free next-generation DFS (Medtronic), that could provide healing without adverse polymer effects and provide controlled and sustained drug elution similar to current-generation DES technology.

How was the RevElution trial designed?

SW: The RevElution trial involves 100 patients, of which I treated 26 patients across two centres in Australia. Per protocol, patients were evaluated using optical coherent tomographic (OCT) imaging and high resolution intravascular imaging to look at tissue coverage as the surrogate marker for healing around the stent strut at an early time-point, in order to detect early healing. The trial also used an angiographic 9-month primary efficacy endpoint of in stent late lumen loss for the first 50 of the patient cohort, which has been a very important surrogate marker for efficacy. The trial has a non-inferiority design and uses a historical comparator of in-stent late lumen loss from the US RESOLUTE trial.

AA: Myself and Professor Worthley are the co-principal investigators of the RevElution trial,



which had investigators participating from around the world to help with trial design, adjudication and interim analysis. This first-in-human trial has a robust study design, and is used to evaluate how patients respond to the technology in terms of healing. To this end, healing in the RevElution trial had to be documented from early on in the procedure, at 30 days, followed by continued assessment at multiple time points up to either 9 or 24 months, depending on the patient cohort. I recruited 10 patients to the trial at my centre in Brazil, whom according to protocol had mostly simple lesions with a single path of disease and relatively focal stenosis.

What are the key published data of the RevElution trial?

SW: Data from the first 50 patients in the 9-month arm of the trial were released as a late-breaker at TCT 2016 with simultaneous publication in the JACC.[1] In-stent late lumen loss was 0.26 mm for the polymer-free DFS, which was lower numerically but statistically non-inferior to the historical control (Figure 2).[1] This late loss is consistent with the late loss seen with other first in human trials.[2] Although RevElution is a small first-in-human trial, results so far have shown that the polymer-free DFS is as efficacious as the current-generation platforms and provides excellent suppression of neointimal hyperplasia, therefore reducing restenosis. Already, we are getting some early signals from the in-stent late lumen loss data that healing may even be better than what we have seen with polymeric-based DES.

A key secondary endpoint of the trial is strut coverage, assessed using OCT. At 1 month, there was already over 91% strut coverage, which is very high.[1] There is a lack of comparative information

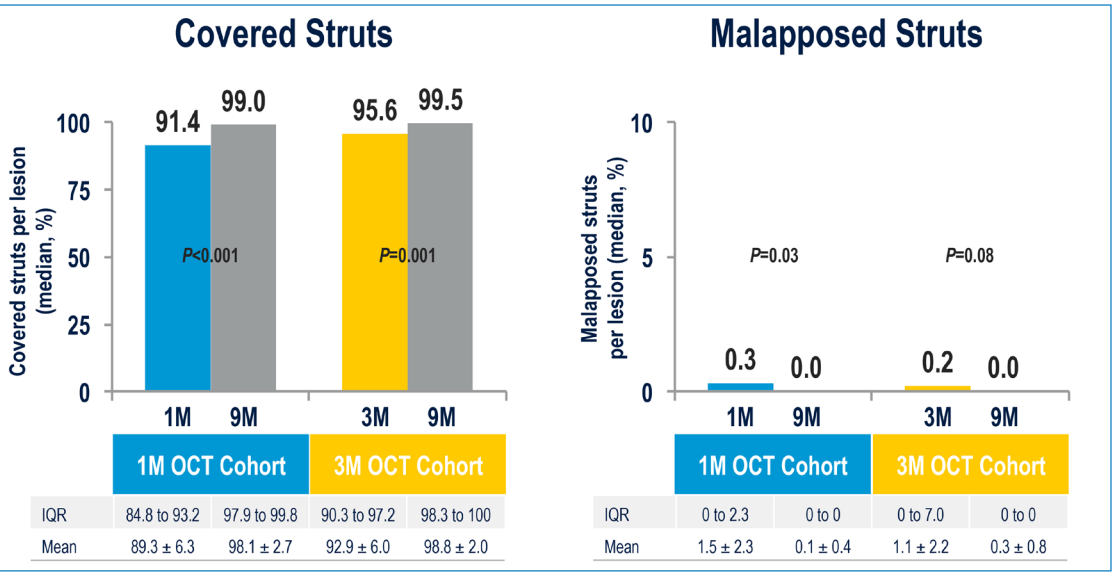
fig. 3

OCT results at 1, 3 and 9 months.

1 month: n=14 patients, 17 lesions, 19 stents, 605 cross-sections and 7403 struts analysed.

3 months: n=15 patients, 17 lesions, 19 stents, 651 cross-sections and 7451 struts analysed.

9 months: n=25 patients, 29 lesions, 32 stents, 1102 cross-sections and 12819 struts analysed.



using high-level imaging techniques, but results from other current-generation stents, such as the XIENCE™ stent, have suggested a 70 or 80% strut coverage at 3 months. For comparison, stent strut coverage in bare metal stents is reported to be in excess of 90% at 1 month.[3] Median coverage increased to 96% at 3 months and 99% at 9 months, with imaging also showing no late-stent malapposition through 9 months (Figure 3).[1] These findings add together to form a very favourable healing profile.

AA: Strut coverage is important; where a lot of strut exposure is not covered, the likelihood of stent thrombosis is higher.[4] When you have more than 90% coverage at 1 month, as observed here, the rationale is that there would be a lower risk of adverse events if DAPT needed to be stopped before 6–12 months.

SW: With regard to adverse events, an important clinical observation was that there have been no stent thromboses and no binary restenosis events so far, but the patient numbers are small. At 9 months, the target lesion failure rate was 2.1%. This equates to a single patient who had a non-ST elevation myocardial infarction (STEMI) event, as adjudicated by our core lab. Overall, even in this small patient cohort, the lack of significant clinical adverse events is very pleasing.

How did these results compare with your expectations?

SW: If anything, the results surpassed my expectations. From an efficacy perspective, I was aiming for the low in-stent late lumen loss that we achieved, but a median stent strut coverage over 90% at 1 month was a pleasant surprise.

When looking at the cumulative distribution curve for in-stent late lumen loss, it is interesting to observe a tight clustering of lumen losses.[1] This attests to the fact that there is a very predictable, consistent healing process. Some cumulative distribution curves often display a tail where a number of patients might have a high late lumen loss; however, that was not shown in this trial. In fact, no patient had even a 1 mm in-stent late lumen loss, so healing was very tightly clustered.

In terms of interpreting these results, one of the things we know is that polymers can become damaged by the introduction of the stent into the coronary artery, which can lead to the polymer peeling or scraping off. As the polymer is used to deliver the drug, this damage may prevent drug delivery in some small areas in the stent. With the next-generation stent platform used in this trial, the drug is protected on the inside of the stent, removing the risk of drug loss due to damage to the coating; this optimises delivery in tortuous or calcified lesions and helps to ensure that drug delivery remains homogeneous.

What are the characteristics of lesions you have been treating?

SW: RevElution is a first-in-human trial by design, and therefore, has relatively simple lesion characteristics. It would be unfair to suggest that we have tested ease of deliverability in really challenging lesions; however, there was some

complexity in the trial. Approximately three quarters of the lesions were B2 or C lesions, so this added some extra complexity and the results were still positive. We excluded chronic total occlusions, aorta ostial lesions and STEMI.

Have any particular patient cases stood out for you?

SW: Yes, one of our patients had a highly tortuous venous vessel beyond the lesion, but remained within the inclusion criteria. When we pre-dilated the lesion, there was a small injury beyond the lesion. We deployed a stent that extended more distally than initially intended, and was deployed around a very tortuous part of the coronary artery. When straightened out, a significant part of the stent hadn't apposed the vessel wall, despite aggressive post-dilatation, which would have been of particular concern if treating with a current-generation DES. However, with the use of the DFS, the patient showed fantastic tissue coverage at 1 month, especially with healing shown around the section of the stent that we were unable to appose to the vessel wall.

Additionally, one of our early patients had to have overlapping stents because of a significant dissection at the proximal end when the first stent was delivered. The 1-month OCT follow-up already showed that there was tissue coverage over the entire region of the overlap. Both cases from our 1-month OCT dataset provide really strong evidence that this healing signal is strong and something that I am actually observing in patients.

How do you expect the positive outcomes with the DFS to impact the duration of DAPT?

SW: In this trial we mandated that patients should stay on DAPT for at least 6 months, with the therapy clinically indicated thereafter. We had very high compliance and all patients were still on DAPT at 6 months. This sets the scene for the design of a short duration DAPT trial, around which there is currently a very active discussion with the FDA and the executive committee. Unless patients have a clinical indication for being on DAPT for longer, a 1-month DAPT duration may be an appropriate duration.

AA: There is a percentage of patients for whom stopping DAPT early could improve safety. These include those who are prone to more bleeding, those scheduled to undergo surgery, who are elderly, have cancer or use anticoagulants. We cannot use our results to immediately start prescribing a 1-month duration of DAPT therapy for all patients. However, in this regard, our trial is a hypothesis-generating trial that can really help us set a rationale for a larger, more robust investigation into the clinical safety of prescribing a short duration of DAPT.

How do results from the RevElution trial compare to other recent studies of bioabsorbable and polymer-based stents, such as ABSORB Japan and the bioabsorbable studies?

SW: I think the data from this trial compare very favourably. When we look at the recent data in the bioabsorbable space – notably data from ABSORB III and 2-year data from ABSORB II – we continue to see the stent thromboses rate and myocardial infarction rates being higher in the patient group that are getting the bioabsorbable platform versus the durable polymer. In those cases the comparator is a XIENCE™ stent.

So what we are seeing with the current dataset from the ABSORB trials is a numeric detriment in the early term with regards to healing. At the moment, I think the detriment that we are seeing is too great for this generation of bioabsorbable stents to be a workhorse stent. However, there will be further iterations in bioabsorbable technology and I have no doubt that they will improve; they will get thinner, they will change the reabsorption kinetics. In the near future, a non-polymeric platform, such as the polymer-free DFS stent, is likely to fill the current unmet clinical need.

How have polymer-free devices been received?

AA: There is still some scepticism in the medical community regarding polymer-free technology. Studies have shown that polymers can be used to control drug release, which generally yields a very strong biological effect to inhibit restenosis and excess neointimal formation. Additionally, late lumen loss with the current generation of polymeric-DES has been shown to be very low, so overall they are regarded as very efficacious. Physicians were scared in the beginning to ask "if there is no polymer with these polymer-free devices, how can you be sure that you are going to have efficacy?" However, similar stents were piloted over 10 years ago,[5] and now we have

the RevElution 9-month data showing a robust elution profile and strong efficacy data. Along with experience in larger randomised trials, such as BioFreedom and the LEADERS FREE trial, the literature is showing that the polymer-free devices are not only safer, but can also be more efficacious.

What are the next steps of the RevElution trial?

SW: What we presented in JACC is the first-half of the RevElution trial, which is the 9-month primary endpoint data in 50 patients,[1] but there is a second cohort that will have 24-month follow-up, so we will continue to follow those patients. Certainly, the 9-month dataset gives us enough evidence to be able to design the next trial, which for me is an appropriately selected patient subset looking at very short duration of DAPT in patients that didn't have a clinical indication to be on a longer duration, as I mentioned previously. It is worth remembering, however, that we mandated in the trial protocol that all patients were to stay on DAPT for at least 6 months and then at the discretion of the treating clinician thereafter. At 1 month, all patients were on DAPT and at 9 months 93.8% were on DAPT

What do you think are the potential implications of your results for patients?

AA: The RevElution trial has shown DFS to be a very promising device so far, with the use of a very smart trial design to draw some very encouraging data based on the OCT results. Although too early to draw definitive conclusions, we have seen a high standard of drug delivery from the DFS. For me, the results show that it is important to have an excellent platform and very clean strut technique with a device that releases medication without a polymer. I think that polymer-free devices such as the DFS are going to be particularly important for patients with high risks of bleeding, using the rationale that you may be able to safely stop DAPT early on at 30 days. Next, we need to assess long-term results at 24-month follow-up, and see if our findings here can be replicated in larger trials with a greater number of patients.

SW: In 5 years' time I would like to see a 'workhorse', easy-to-use, simple stent platform that has as good efficacy as any stent platform that we currently use in terms of neointimal suppression and reducing restenosis, and yet may support very short DAPT, potentially for 1 month. If antiplatelet therapy has to be stopped early, we need to feel safe doing so. For patients that might be at higher risk of stent thrombosis or a complication, like chronic total occlusions or even STEMIs for example, the favourable healing with DFS may give an improved safety signal.

The results of RevElution are very exciting, albeit preliminary. We don't want to get too ahead of ourselves with the information we have, because we currently only have data on 50 patients. Current data confirm that we have an efficacious platform, as shown in surrogate OCT imaging, which showed early healing with 91% stent strut coverage at 1 month. We look forward to the further trials and the completion of the RevElution 24-month dataset to confirm that, indeed, the safety signals of the early healing profile actually lead to improvement in a clinical outcome. When we have more data and are confident in the technology I can absolutely see this DFS platform being the next 'workhorse' for the DES.

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