Stephen Lee

Early stent healing and late neointima progression with second generation drug-eluting stents: The OCT-ORION Study

Drug-eluting stents have become a mainstay for percutaneous coronary intervention. Second- and third-generation stents have shifted in focus towards the removal of the polymer, with the development of 'bio-absorbable' and 'polymer-free' options, which aim to improve stent healing. *Confluence* spoke to Professor Stephen Lee of Queen Mary Hospital, University of Hong Kong, about the OCT-ORION study, which compared the efficacy of bio-absorbable and durable polymer stents using a new protocol for assessing the impact of these stents on lesion healing in patients with coronary disease.

What is the current standard of treatment for patients with severe coronary lesions?

Professor Stephen Lee (SL): In the last 20 years, patients with severe coronary lesions have predominantly been treated via a percutaneous approach, as an alternative to bypass surgery. In general, 'stenting' is the main method for treating patients with coronary disease and this is the only remaining procedure that can greatly improve patient outcomes when compared to surgery. I think that its use for the treatment of coronary disease will likely remain popular for at least the next 10–20 years; other devices may come and go, but they are unlikely to be as effective or safe when compared to stenting via the percutaneous approaches being used now.

The stent itself has gone through several different stages of development. Traditional bare-metal stents are still used, but nowadays physicians also have access to the newer generations of 'bio-absorbable' or 'bioresorbable' stents, in addition to the popular drug-eluting stents (DES), which deliver a range of anti-proliferative drugs through the use of a polymer, or via a mechanism on the stent surface that allows delivery without a polymer.

What led to the development of bio-absorbable polymers?

SL: The rationale behind the development of bio-absorbable polymers stemmed from a school of thinking that suggested that by removing the polymer, patient outcomes could hopefully be improved by avoiding associated hypersensitivity reactions and inflammation, which lead to non-healing.[1] As the slow release of the antiproliferative drug from a polymer carrier is essential to suppress neointimal proliferation, the development of a polymer that degrades and disappears within a couple of months could be an attractive alternative to prevent hypersensitivity reactions.

As well as bio-absorbable polymers, the newer generation of stents include those that are completely polymer free. There have been high hopes that these new stents will lead to improved results, but currently approved polymer-free DES have limitations, such as quick drug lease. So far, it has never been proven that the bio-absorbable polymer DES, or even the polymer free ones are a better option than the durable polymer.

What is the ultimate goal of stenting?

SL: Ultimately, the goal is to have a stent that could be implanted into the patient without ill effect in terms of healing. We know that in the long term stents may end up in late stent failure, which could be due to stent thrombosis from non-healing, excessive proliferation due to neoatherosclerosis or perhaps a hypersensitive response.[2] We are hoping to develop some stents that could accelerate healing and at the same time deliver the drug to suppress the neointimal proliferation, but this ideal stent doesn't yet exist.

Proper healing occurs when the stent surface is covered by true endothelium, inhibiting signalling pathways to prevent the smooth muscle cells from continuing to migrate and proliferate, reducing the

neointimal hyperplasia. At the same time, stent thrombosis is lowered when the stents are fully covered.

What is the rationale behind the OCT-ORION study?

SL: The OCT-ORION study is the first study to observe a head-to-head comparison between stents with a bio-absorbable and a durable polymer, using the same individual patient as his/her own control. The study aimed to evaluate the impact of polymers on patients in terms of early healing and 9 months safety and efficacy, and whether outcomes would significantly improve when the polymer is removed.

Two well-known second-generation stents were used: the Medtronic Resolute Integrity™ Zotarolimus-Eluting Coronary stent and the Biosensors BioMatrix NeoFlex™ stent. The Resolute Integrity™ stent from Medtronic is well proven and has a durable BioLinx-only polymer specifically designed for DES, which elutes zotarolimus with a low inflammatory score. The BioMatrix™ stent from Biosensors International makes use of a polylactic acid (PLA) bio-absorbable polymer that elutes Biolimus A9™ as its antiproliferative drug. Both of these stents have been used in our centre for several years.

How was the study designed?

SL: The study was designed to enrol 60 patient all-comers with critical stenoses on 2 to 3 coronary vessels. The main exclusion criterion was patients with ST Segment Elevation Myocardial Infarction (STEMI). Patients received both stents, one on each vessel, enabling them to act as their own control which reduced the impact of confounding factors. We were able to achieve 100% patient follow-up throughout.

The study design was based around healing; the more that the stent is covered by neointimal tissue (perhaps endothelium), the more healing we have. Early healing was assessed by using longitudinal sequential optical coherence tomography (OCT) to calculate the extent of stent coverage at 2–6 months with the use of a very stringent six-category classification. For the early stent strut coverage, we postulated BioMatrix™ to perform better than Resolute Integrity™, as the former has a polymer which degrades in few months, possibly allowing for faster healing. We also looked at neointimal progression at mid-term at around 9 months, which we postulated would be lower in the Resolute Integrity™ stent due to longer eluting times of zotarolimus, which takes almost 180 days to completely elute.

The different types of limus used by each stent is the most important concern. However, when the study was first conducted 3 years ago, there were no bio absorbable or durable polymer stents produced by the same company using the same eluting drug. At best, both of the stents we used are comparable second-generation DES and the study factored in both the efficacy and equivalent dosage for the clinical setting. As the same drug is not used in both stents, we expect to see some differences; this was something we could not address, but for the purpose of this study, our aim was to evaluate the impact of the polymer as well as we possibly could.

How was OCT used a measure of healing?

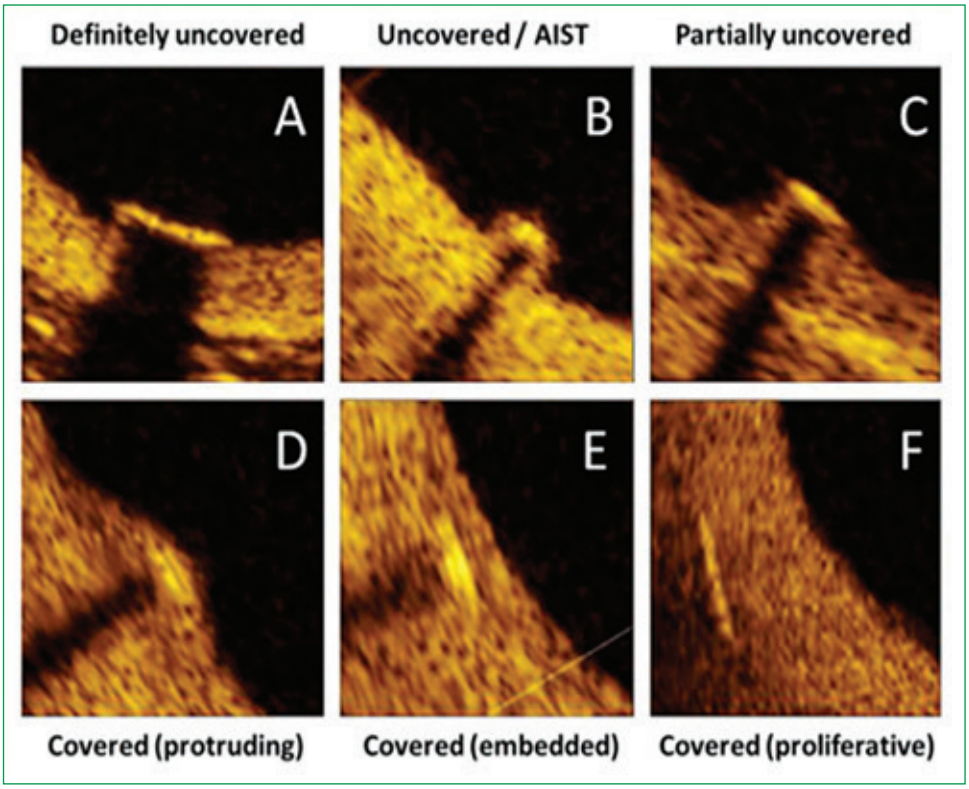
SL: Imaging with OCT has only become available for use in the last few years and is still not accessible in a large number of centres. OCT imaging was used in 100% of all patients and all follow-ups in this study. The beauty of OCT is that the resolution is very high, dropping down to as low as 10 microns, equating to about three cell layers. This resolution is never achievable with intravascular ultrasound (IVUS), which is about 10 times less sensitive. For both angiograms and IVUS, early stent coverage cannot be seen at all. Therefore, OCT was the only way to quantify such a minute degree of stent coverage in terms of just a few cell layers in the early phases of several months. The longitudinal sequential OCT protocol used could provide maximum information on the safety and efficacy *in vivo*, as well as monitor the transformation and maturation of the neointima.

An important benefit of OCT is that it gives a vast amount of data from just a small sample size. Each frame is only 0.2 mm thick (5 frames per mm); a regular 18 mm long stent will give you 90 frames, and within each frame there are roughly 10–12 struts. Therefore, for each patient, we expected over 100 frames and 1000 struts per stent arm, and both stent arms can be compared directly with each other. This provided us with a large amount of solid data that was very revealing. The combination of high resolution and the sheer volume of data that OCT can collect from the analysis is why it was the method of choice.

fig. 1

Categorisation of strut coverage.

A, B & C represent uncovered struts D, E & F represent covered struts.



To obtain data using OCT, all struts are counted in a frame-by-frame manner. The OCT computer can be used to directly measure the neointimal coverage, as well as its thickness, cross-sectional area and volume. Figure 1 displays the working classification for strut coverage that we have generated for the study. The A, B and C panels are categorised as uncovered or partially uncovered, and the D, E and F struts are covered. This classification works to ensure that the results will be consistent and visually reproducible. All these analyses were processed in a blind fashion by the core lab of the Cardiovascular Research Foundation, New York, USA.

What do the results from this study show?

SL: Results from the study assessed early stent coverage and mid-term stent coverage, as well as neointimal progression. As I have said previously, from the stent design we expected to see BioMatrix™ perform better during the early

fig. 2

Early strut coverage (2–6 months) of BioMatrix™ and Resolute Integrity™.

Blue points correspond to BioMatrix™; red points correspond to Resolute Integrity™.

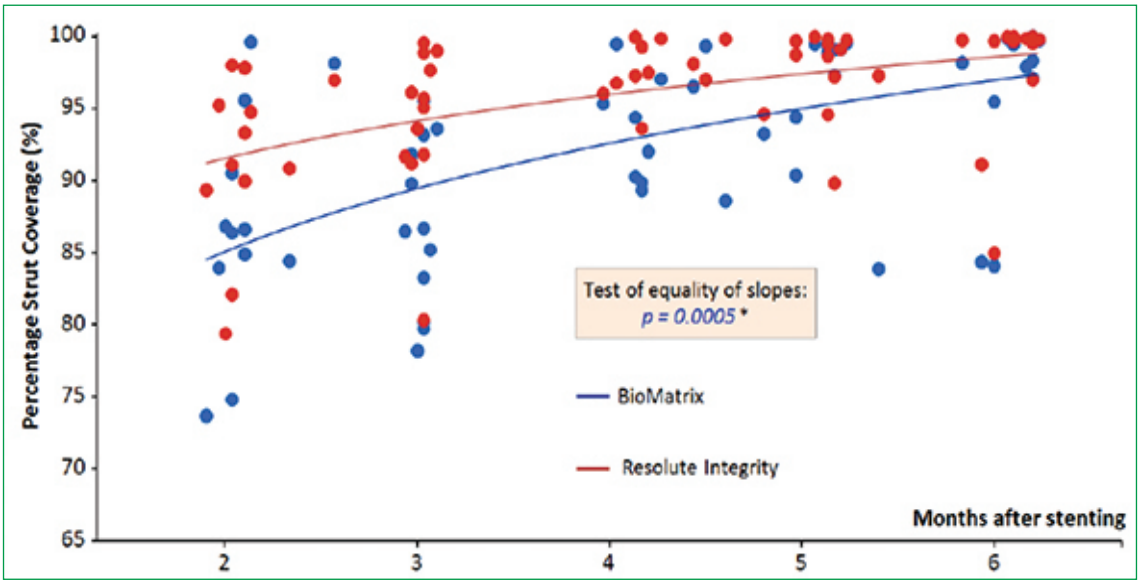
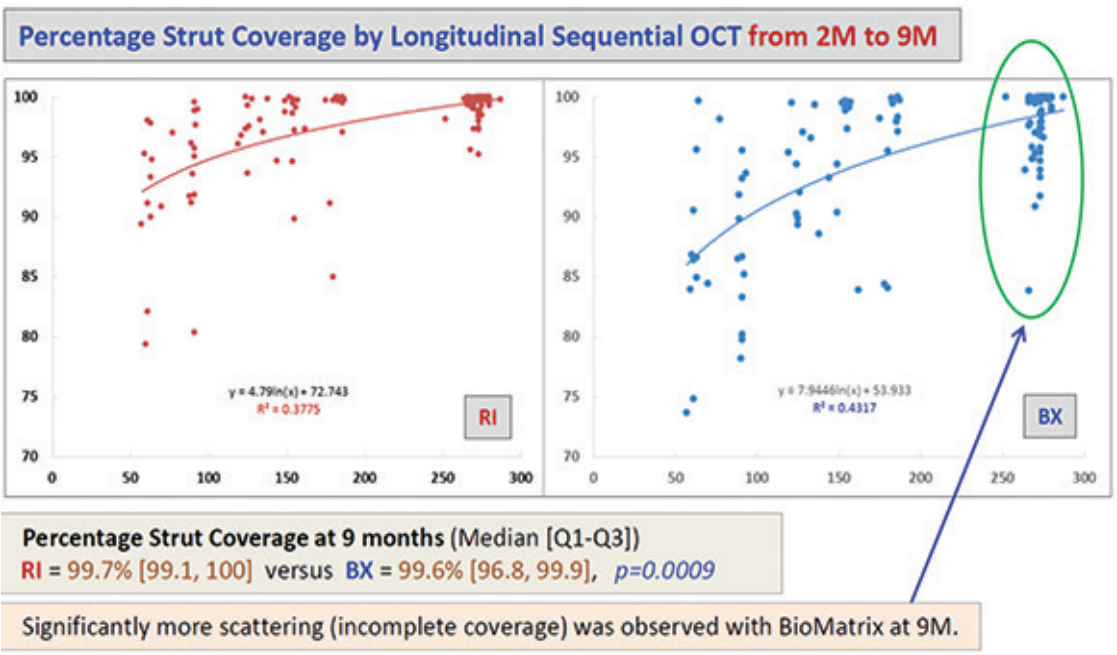


fig. 3

Mid-term strut coverage (2–9 months).

Left scatter plot (red) represents data from Resolute Integrity. Right scatter plot (blue) represents data from BioMatrix™. X Axis: time (days). Y Axis: strut coverage (%).



period of 2–6 months due to the absence of the polymer. Yet, contrary to the postulation, it was Resolute Integrity™ with the durable polymer that yielded a better healing profile. We were also surprised to see that Resolute Integrity™ had far less scattering than BioMatrix™, in addition to a better healing curve with a higher percentage of strut coverage (figure 2).

While both stents initially showed a large amount of scattering – such as at 60 days where only a few patients had more than 95% coverage (figure 3) – by 90 days, and through to 200 days, the scattering reduced as the coverage improved and percentage strut coverage increased. By the mid-term results of 9 months, both stents eventually approached 99–100% strut coverage. However, BioMatrix™ showed a much larger variance in results by 9 months, as highlighted by the increased scattering in the green oval in figure 3. Patients with a lower percentage strut coverage by 9 months – around 85% – could be more at risk of having complications, such as stent thrombosis, and could have a less ideal performance long term. Once again, the extent of healing observed with BioMatrix™ was not as complete as with Resolute Integrity™ at all time frames.

In terms of safety and efficacy, both stents showed comparable neointimal suppression with other reported series of DES studies. Quantitative coronary angiography reflected that patients had a very low target vessel revascularisation rate and very low binary restenosis percentages at less than 5%.

The predominant inclusion criterion for the study was advanced disease with critical stenosis in 2 to 3 vessels, and it was no surprise that over half of the patients included in the trial had diabetes. Within this diabetic patient subgroup, the Resolute Integrity™ stent also yielded significantly better results in early 6 months compared with BioMatrix™ (p=0.0016).

How do results compare with other studies which have looked at bio-absorbable polymers?

SL: It is hard to compare our results with other studies that have evaluated the performance of bio-absorbable polymers, as the study designs are dissimilar. Not many other studies have used a longitudinal sequential OCT protocol nor reported findings for the earlier months.

What are the main conclusions from the OCT-ORION study?

SL: My conclusion from the results is that the bio-absorbable polymer, BioMatrix™, contrary to the postulation, doesn't seem to offer any benefit over the use of the durable polymer, Resolute Integrity™. The solid OCT evidence of lower performance of BioMatrix™ for both early-month and 9-month data suggests that a bio-absorbable polymer is not essential, as shown by direct comparison between

the two stents in the same patient. However, it could be argued that the Biolimus A9™ drug is too dissimilar to zotarolimus, and, therefore, some of the differences seen could be due to efficacy variations between the drugs used, rather than the impact of the polymer. However, in terms of clinical practice, I would still expect to observe better performance with the use of Resolute Integrity™.

What implications do you think these results will have on stenting in the future, particularly regarding the use of bio-absorbable polymers?

SL: Importantly, I think of our study as a pilot study for proof of concept and stent comparison in patients with at least two-vessel disease. My hope is that this kind of protocol may be surrogated to other stent studies and act as a *de novo* protocol for observing healing in the early months, as well as monitoring healthy neointimal transformation by 9 months, or even up to 24 months. This type of trial can be redesigned in many ways, for example into a non-inferiority or superiority end-point, depending on what you want to observe. However, the standard of performing percutaneous coronary intervention and OCT in the study centres needs to be high because repeating the OCT follow-ups three times in a single patient could mean a high operation risk. The risk of the OCT pull-back procedure, and the risk of contrast load for diabetic patients have to be taken into account.

With such a huge amount of solid data from a relatively small sample size, we hope that with longitudinal sequential OCT follow-ups we might be able to assess any new stent platforms with a much smaller sample size and in a much shorter time frame. This could allow us to achieve better predictions regarding safety and efficacy as claimed by any new stent platforms. Hopefully this will benefit our patients in the long term.

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REFERENCES:

1. Nebeker JR, et al. *J Am Coll Cardiol* 2006; 3;47(1):175–81
2. Joner, M. Presented at *European Society of Cardiology Congress 2015, Barcelona, Spain.*

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