

Is a biodegradable polymer stent really superior to a durable polymer stent?



Huay Cheem Tan^{1,2}, MBBS; Joshua P. Loh^{1,2*}, MBBS

1. Department of Cardiology, National University Heart Centre, Singapore, Singapore; 2. Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

While first-generation drug-eluting stents (DES) with durable polymers have been shown to be effective in reducing angiographic and clinical restenosis compared with bare metal stents, they were beset with problems of late and very late stent thrombosis attributed to delayed healing and re-endothelialisation¹. The durable polymer (DP) coatings are deemed to play an important causative role in inciting chronic inflammatory reaction in the vascular wall, leading to late events². The recently developed biodegradable polymer (BP)-coated DES, which offer similar or better control of drug delivery and release dynamics (without the long-term sequelae of durable polymer), are theoretically superior to DES with durable polymer coatings in reducing long-term adverse events. They aim to combine the efficacy of DES with the long-term safety of a bare metal stent.

There are various BP-DES on the market, ranging from the early bulky stainless steel stents, such as the biolimus-eluting BioMatrix™ stent (Biosensors, Morges, Switzerland), to new cobalt-chromium stents such as the sirolimus-eluting Ultimaster® (Terumo Corp., Tokyo, Japan) and Orsiro (Biotronik AG, Bülach,

Switzerland) stents, and the everolimus-eluting platinum-chromium SYNERGY™ stent (Boston Scientific, Marlborough, MA, USA). Polymer degradation can range from three to four months to over 12 months. In general, there are three types of synthetic biodegradable polymer: polyglycolic acid (PGA), polylactic acid (PLA) and poly glycolic-co-lactic acid (PLGA). PLA and PGA have lactic acid and glycolic acid that are ultimately converted to water and carbon dioxide through the action of enzymes in the tricarboxylic acid cycle and excreted via the respiratory system. PLA is more resistant to hydrolytic attack than PGA and increasing the PLA:PGA ratio in the PLGA copolymer will result in delayed degradability³.

The strongest purported benefit of biodegradable polymer stents is the fact that there is complete dissolution of the polymer after one year with no residual drug to cause persistent long-term vascular inflammation. Numerous studies have been performed to compare the efficacy and safety of BP-DES versus DP-DES. The first such comparator study was that of a BP biolimus-eluting stent (BES) (BioMatrix) with the CYPHER® stent (Cordis, Cardinal Health, Milpitas, CA, USA) in the LEADERS trial⁴. While similar

*Corresponding author: Department of Cardiology, National University Heart Centre, Kent Ridge Road, NUHS Tower Block, Level 9, Singapore 119228, Singapore. E-mail: Joshua_PY_Loh@nuhs.edu.sg

rates of the composite endpoint of cardiac death, myocardial infarction (MI), and clinically indicated target vessel revascularisation (TVR) were observed within nine months of DES implantation (9.2% with BP-BES versus 10.5% with DP-SES; *p* for non-inferiority=0.003), there was a numerically lower incidence of the primary endpoint with BP-BES vs. SES (22.3% vs. 26.1%, *p* for non-inferiority <0.0001, *p* for superiority=0.069) at five years⁵. There was also a significant reduction in very late definite ST from one to five years with BES vs. SES (0.7% vs. 2.5%, *p*=0.003).

In this issue of AsiaIntervention, Chung et al⁶ compared a BP sirolimus-eluting stent (Orsiro) with a durable polymer, sirolimus-eluting stent (CYPHER) to determine if late failure of the CYPHER is caused by the polymer or sirolimus.

Article, see page 77

The results showed that, at two years of follow-up, the composite outcome of cardiac death, stent thrombosis, and clinically driven target lesion revascularisation (TLR) occurred in 3.0% of the Orsiro group and 9.6% of the CYPHER group.

Among the 344 (79.9%) patients who were followed up from nine months to two years, stent failure occurred significantly less in the BP-SES group than in the DP-SES group (1.6% vs. 7.7%, HR 0.25, 95% CI: 0.06–0.74, *p*=0.011). The investigators performed multivariable Cox regression analysis which showed that the Orsiro stent was a significant independent predictor of clinical events two years after PCI. They concluded that late CYPHER failure is attributable to its durable polymer and not to the antiproliferative drug sirolimus, since both DES share the same drug.

The conclusion of this study could be somewhat questionable, as it is too simplistic to attribute the difference in stent failure rates to mere differences in the type of polymer coating, namely durable vs. biodegradable polymer. The two stents share the same type of drug and concentration (1.4 µg/mm²) but differ in all other aspects including the types of polymer, stent alloy used, stent design, stent strut thickness and drug elution kinetics, with each of these characteristics having the potential to impact on the clinical performance of a stent.

It is known that, among the many BP-DES on the market, they differ in terms of their clinical performance. BP-BES were shown to have a higher incidence of stent thrombosis compared to a cobalt-chromium everolimus-eluting stent (Co-Cr EES)⁷. This was attributed to the thin-strut backbone of 81 µm for the EES and its novel polymeric drug carrier which consists of a non-inflammatory ultrapure fluorinated copolymer versus the thick struts of the BP-DES stainless steel design⁸.

Early studies in the bare metal stent (BMS) era had conclusively demonstrated that thin-strut stents fared better than thick-strut stents in reducing the restenosis and target vessel revascularisation rates^{9,10}. In the SORT OUT VII study which compared the thin-strut BP sirolimus-eluting Orsiro stent versus the thick-strut BP biolimus-eluting Nobori[®] stent (Terumo Corp.) in unselected patients, the Orsiro stent was associated with a reduced risk of definite stent thrombosis (0.4% vs. 1.2%, *p*=0.03)¹¹. In a comparison of the thin-strut BP-SES Orsiro with the thin-strut Pt-Cr EES

SYNERGY stent and a thin-strut DP zotarolimus-eluting stent (ZES) in the BIORESORT trial, the target lesion failure rate at 12 months was 4% for the patients treated with a BP-DES (either the SES Orsiro stent or the EES SYNERGY stent) versus 5.0% for the DP-ZES, which was not significant¹². A recent meta-analysis of 16 randomised controlled trials comparing BP-DES with second-generation DP-DES demonstrated similar safety and efficacy profiles, even after accounting for the type of antiproliferative drug used, stent platform, kinetics of polymer degradation/drug release, strut thickness, and duration of dual antiplatelet therapy¹³.

While all comparator studies of the new generation of thin-strut BP-DES showed clinical parity with second-generation EES, one exception was the BIOFLOW V trial. This study showed that the BP-SES Orsiro outperformed Co-Cr EES in 1,334 randomised patients with a significant reduction in target lesion failure rates (4% vs. 7%, *p*=0.03). The difference was observed as early as 30 days, predominantly driven by a difference in MI. At the 12-month primary endpoint, target lesion failure was 6% in the BP-DES group versus 10% in the DP-DES group, *p*=0.04¹⁴. Despite the positive results seen in favour of BP-SES, one has to be cautious in attributing this to the biodegradable polymer concept. The higher incidence of MI observed for Orsiro versus XIENCE (Abbott Vascular, Santa Clara, CA, USA) (5% vs. 8%, *p*=0.0155) was most likely due to a tighter definition of MI compared with other studies and the ultrathin-strut design of the Orsiro stent. The true litmus test of the Orsiro with its biodegradable polymer will only be known in a long-term follow-up study when the biodegradable polymer is fully resorbed after one year.

Given the many variables among different DES, the results of any direct comparator studies can only apply to the stents being studied. One can only conclude from Chung et al's study that the Orsiro stent performed better than the first-generation CYPHER stent in safety and efficacy because of its inherent design. The exact component driving the difference in outcomes remains speculative and is probably multifactorial, something which cannot be fully answered in this study.

Biodegradable polymer technology with its potential to reduce vessel inflammation and consequent neoatherosclerosis, late stent thrombosis and restenosis will continue to generate interest in the field. Whether this will be transformed into safety benefit in the long term needs to be validated in longer and larger studies. Until then, we can be sure that there will be many such comparator studies carried out.

Conflict of interest statement

J.P. Loh and H.C. Tan report research funding from Boston Scientific.

References

- Iglesias JF, Roffi M, Degrauwe S, Secco GG, Aminian A, Windecker S, Pilgrim T. Orsiro cobalt-chromium sirolimus-eluting stent: present and future perspectives. *Expert Rev Med Devices*. 2017;14:773-88.

2. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004;364:1519-21.
3. Commandeur S, van Beusekom HM, van der Giessen WJ. Polymers, drug release, and drug-eluting stents. *J Interv Cardiol*. 2006;19:500-6.
4. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Jüni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet*. 2008;372:1163-73.
5. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, Rademaker-Havinga T, van Es GA, Meier B, Jüni P, Windecker S. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) randomized, noninferiority trial. *JACC Cardiovasc Interv*. 2013;6:777-89.
6. Chung JH, Lim WH, Kim HL, Seo JB, Chung WY. Long-term clinical outcomes with biodegradable polymer sirolimus-eluting stents versus durable polymer sirolimus-eluting stents. *AsiaIntervention*. 2018;4:77-86.
7. Palmerini T, Biondi-Zoccai G, Della Riva D, Mariani A, Sabaté M, Smits PC, Kaiser C, D'Ascenzo F, Frati G, Mancone M, Genereux P, Stone GW. Clinical outcomes with bioabsorbable polymer- versus durable polymer-based drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol*. 2014;63:299-307.
8. Serruys PW, Ong AT, Piek JJ, Neumann FJ, van der Giessen WJ, Wiemer M, Zeiher A, Grube E, Haase J, Thuesen L, Hamm C, Otto-Terlouw PC. A randomized comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: the SPIRIT first trial. *EuroIntervention*. 2005;1:58-65.
9. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schühlen H, Neumann FJ, Fleckenstein M, Pfaffert C, Seyfarth M, Schömig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circulation*. 2001;103:2816-21.
10. Pache J, Kastrati A, Mehilli J, Schühlen H, Dotzer F, Hausleiter J, Fleckenstein M, Neumann FJ, Sattelberger U, Schmitt C, Müller M, Dirschinger J, Schömig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. *J Am Coll Cardiol*. 2003;41:1283-8.
11. Jensen LO, Thayssen P, Maeng M, Ravkilde J, Krusell LR, Raungaard B, Junker A, Terkelsen CJ, Veien KT, Villadsen AB, Kalsoft A, Tilsted HH, Hansen KN, Aaroe J, Kristensen SD, Hansen HS, Jensen SE, Madsen M, Bøtker HE, Berencsi K, Lassen JF, Christiansen EH. Randomized Comparison of a Biodegradable Polymer Ultrathin Strut Sirolimus-Eluting Stent with a Biodegradable Polymer Biolimus-Eluting Stent in Patients Treated with Percutaneous Coronary Intervention: The SORT OUT VII Trial. *Circ Cardiovasc Interv*. 2016 Jul;9(7).
12. von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, Gin RMTJ, Somi S, van Houwelingen KG, Stoel MG, de Man FFAF, Louwerenburg JHW, Hartmann M, Zocca P, Linssen GCM, van der Palen J, Doggen CJM, Löwik MM. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. *Lancet*. 2016;388:2607-17.
13. El-Hayek G, Bangalore S, Casso Dominguez A, Devireddy C, Jaber W, Kumar G, Mavromatis K, Tamis-Holland J, Samady H. Meta-Analysis of Randomized Clinical Trials Comparing Biodegradable Polymer Drug-Eluting Stent to Second-Generation Durable Polymer Drug-Eluting Stents. *JACC Cardiovasc Interv*. 2017;10:462-73.
14. Kandzari DE, Mauri L, Koolen JJ, Massaro JM, Doros G, Garcia-Garcia HM, Bennett J, Roguin A, Gharib EG, Cutlip DE, Waksman R; BIOFLOW V Investigators. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. *Lancet*. 2017;390:1843-52.