EuroIntervention
2024;20:e625-e626
published online e-edition May 2024
DOI: 10.4244/EIJ-E-24-00017

EDITORIAL

Is this the end of the ultrathin-strut hypothesis?

Sripal Bangalore*[1], MD, MHA; Aloke V. Finn[2,3], MD

**Corresponding author: New York University Grossman School of Medicine, 550 1st Ave., New York, NY, 10016, USA. E-mail: sripalbangalore@gmail.com*

The authors' affiliations can be found at the end of this article.

From Grüntzig first coronary angioplasty to contemporary drug-eluting stents (DES), there has been significant progress in stent technology. A change in the biomaterial used, from stainless steel to cobalt/platinum chromium, has allowed for thinner struts while maintaining radial strength and radiopacity. The strut thickness has been reduced through the generations of thick (>100 µm), thin (70 to 100 µm) to now ultrathin DES (<70 µm)[1]. Preclinical models and human stented arteries demonstrate that strut thickness impacts medial injury and inflammation, leading to higher degrees of neointimal hyperplasia for thicker-strut stents. In parallel with the improvement in strut thickness, stent polymer technology evolved from durable polymers (DP) to biodegradable polymers (BP). However, BP-DES on a thin-strut platform have been at best non-inferior to current-generation DP-DES, and the promise of a late superiority (after bioabsorption of the polymer) has remained elusive[2]. On the other hand, clinical trials and meta-analyses have shown the superiority of ultrathin-strut DES over thin-strut DES[1]. The ultrathin DES have a strut thickness between 50 µm and 65 µm; they use a biodegradable polymer and elute sirolimus. Whether the strut thickness, the biodegradable polymer, the drug or the combination of these are responsible for the superiority has been debated.

Understanding that the outcomes improved according to the timepoint of benefit (early vs late) is the first step to potentially unravelling the mechanistic link. In a meta-analysis of 10 randomised controlled trials (RCTs), at 1-year follow-up, use of ultrathin BP-DES reduced target lesion failure (TLF), driven mainly by lower rates of target vessel myocardial infarction (TVMI), a numerically lower incidence of stent thrombosis, and with no difference in target lesion revascularisation (TLR; risk ratio 0.97, 95% confidence interval: 0.77-1.22)[1]. Additionally, there was no heterogeneity of effect ($p_{interaction}$=0.58) based on the ultrathin DES tested (Orsiro [Biotronik], MiStent [Micell] and BioMime [Meril Life]). In an updated meta-analysis evaluating longer-term follow-up (mean 2.5 years), ultrathin BP-DES reduced TLF, target vessel failure (TVF), definite or probable stent thrombosis, TLR and target vessel revascularisation (TVR)[3]. Among the ultrathin stents, Orsiro is unique in that it is ultrathin (60 µm) for stent sizes ≤3.0 mm but not for sizes >3.0 mm (80 µm). In a prespecified analysis of BIORESORT evaluating 3-year outcomes in small vessels, Orsiro had the lowest rate of TLF (7.5%) versus XIENCE (Abbott; 9.5%) or Resolute (Medtronic; 10.0%). Moreover, TLR was lower with Orsiro versus Resolute, which emerged after the first year of follow-up (1.0% vs 3.7%; p=0.006)[4]. In summary, the early benefit (≤1 year) of ultrathin BP-DES appears to be a reduction in TVMI (driven largely by a reduction in procedural MI) and perhaps stent thrombosis, whereas the late effect (>1 year) seems to be lower rates of TLR and stent thrombosis. The early effect is unlikely to be due to the bioabsorption of polymer, as it takes >12-18 months to bioabsorb.

In this issue of EuroIntervention, Ikegami et al[5] attempt to answer the question of the effect of strut thickness on vessel healing using a clever design which takes advantage of different strut thicknesses (60 µm vs 80 µm) within the Orsiro platform, thus keeping other stent design elements constant. In a small preclinical study of 8 rabbits, using a balloon injury model implanted with either the 80 µm (3.5 mm diameter) or the 60 µm thick stent (3.0 mm diameter), both the ultrathin- and thin-strut BP-DES exhibited similar stent fibrin deposition (p=0.49) and a similar percentage of uncovered struts (p=0.63), suggesting similar healing. Moreover, the majority of struts (>97%) remained uncovered. The authors concluded that features beyond ultrathin-strut thickness may underlie the observed benefits and that further reduction of strut thickness beyond 60 µm may not offer additional clinical advantages.

Article, see page e669

Before we throw the baby out with the bathwater, some considerations are described below. Given that the majority of struts were uncovered in both the thin and ultrathin groups,

the early benefit observed in clinical studies is likely due to factors beyond early differential healing – factors potentially influenced by strut thickness. For example, (1) thinner struts result in more laminar flow; they reduce recirculation and stagnation of blood pool around the strut and have lower thrombogenicity when compared with identical thick-strut stents[6]. Whether this extends to ultrathin stents is not known and cannot be ruled out by the current study. Thus, the lower rates of stent thrombosis (both early and late) observed in the meta-analysis could be explained by this mechanism. 2) Thinner struts cause less vessel wall injury/inflammation. While it is not known if ultrathin stents result in an incremental reduction in wall injury/inflammation, the current study cannot rule it out, and it could explain the reduction in procedural MI seen in RCTs. 3) Moreover, given that the majority of struts were uncovered on day 7 in the rabbit model, a late differential healing (at day 28 or day 90) between the thin versus ultrathin groups cannot be ruled out. First-generation DES showed over 80% strut coverage on day 28 in the rabbit model[7]. The late emergence of lower TLR rates seen in some studies (especially in small vessels) perhaps points to a benefit seen after the polymer bioabsorbs. However, this stands in stark contrast to data from BP-DES on a thin- or a thick-strut platform showing no late benefit after the polymer bioabsorbs[2]. Finally, the clinical outcomes data derived from the *post hoc* analysis are problematic. In the animal model, both the 3.0 mm and 3.5 mm BP-DES were implanted in similar size aorta and postdilated with a 3.5-3.75 mm non-compliant balloon, resulting in similar stent expansion ratios. However, unlike the animal model, the clinical outcomes data merely represent a comparison of small vessels (where 3.0 mm stents were used) versus larger vessels (where 3.5 mm stents were used), and, as such, the early benefit of ultrathin platforms seen in the meta-analysis was not replicated. In the *post hoc* BIOSTEMI outcomes presented, death, cardiac death, TLF, TVF and stent thrombosis at 30 days were paradoxically worse in the ultrathin- (3.0 mm stent) versus the thin-strut (3.5 mm stent) group, while in the overall randomised comparison of ultrathin- (Orsiro) versus thin-strut (XIENCE), the results favoured the ultrathin platform at 30 days.

Where does this leave us with the ultrathin-strut hypothesis? The incremental mechanistic advantage of ultrathin over thin struts can only be fully ascertained by the assessment of inflammation/other markers of vessel injury immediately following implantation; assessment of flow dynamics to evaluate for differential thrombogenic potential prior to vessel healing, and finally, evaluation of vessel healing at a timepoint where there is at least 50% endothelial coverage to assess for differential healing (perhaps at day 28). While using the 3.0 mm versus 3.5 mm stent within the Orsiro platform offers certain advantages, this is at the expense of differential expansion (higher pressure/larger balloon needed in the 3.0 mm group to achieve the same stent expansion ratio as a 3.5 mm stent) and potentially differential injury to the vessel wall. Ongoing trials of ultrathin- versus thin-strut DES will provide additional clinical outcomes for other platforms of ultrathin BP-DES. Until that time, the mechanistic link between superior clinical outcomes and ultrathin-strut DES remains a mystery, but let us not throw the baby out with the bathwater!

Authors' affiliations

1. Division of Cardiology, Department of Medicine, New York University Grossman School of Medicine, New York, NY, USA; 2. CVPath Institute, Gaithersburg, MD, USA; 3. School of Medicine, University of Maryland, Baltimore, MD, USA

Conflict of interest statement

S. Bangalore reports grants and personal fees from Abbott; and personal fees from Boston Scientific, Biotronik, Pfizer, Amgen, Inari, Truvic, ReCor, and Reata, outside of the submitted work. A.V. Finn has received honoraria from Abbott Vascular, Boston Scientific, Medtronic, Cook Medical, BD, and Terumo Corporation.

References

1. Bangalore S, Toklu B, Patel N, Feit F, Stone GW. Newer-Generation Ultrathin Strut Drug-Eluting Stents Versus Older Second-Generation Thicker Strut Drug-Eluting Stents for Coronary Artery Disease. *Circulation.* 2018;138:2216-26.

2. Bangalore S. The Elusive Late Benefit of Biodegradable Polymer Drug-Eluting Stents. *Circulation.* 2019;139:334-6.

3. Madhavan MV, Howard JP, Naqvi A, Ben-Yehuda O, Redfors B, Prasad M, Shahim B, Leon MB, Bangalore S, Stone GW, Ahmad Y. Long-term follow-up after ultrathin vs. conventional 2nd-generation drug-eluting stents: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J.* 2021;42:2643-54.

4. Buiten RA, Ploumen EH, Zocca P, Doggen CJM, van der Heijden LC, Kok MM, Danse PW, Schotborgh CE, Scholte M, de Man FHAF, Linssen GCM, von Birgelen C. Outcomes in Patients Treated With Thin-Strut, Very Thin-Strut, or Ultrathin-Strut Drug-Eluting Stents in Small Coronary Vessels: A Prespecified Analysis of the Randomized BIO-RESORT Trial. *JAMA Cardiol.* 2019;4:659-69.

5. Ikegami R, Piao Z, Iglesias JF, Pilgrim T, Ha K, McCarthy JR, Castellanos MI, Kassab MB, Albagdadi MS, Mauskapf A, Spicer G, Kandzari DE, Edelman ER, Libby P, Heg D, Joner M, Tearney GJ, Jaffer FA. Ultrathin-strut versus thin-strut stent healing and outcomes in preclinical and clinical subjects. *EuroIntervention.* 2024;20:e669-80.

6. Kolandaivelu K, Swaminathan R, Gibson WJ, Kolachalama VB, Nguyen-Ehrenreich KL, Giddings VL, Coleman L, Wong GK, Edelman ER. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation.* 2011;123:1400-9.

7. Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation.* 2005;112:270-8.