Editorial

Walking the right path: the story of bioresorbable stents

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He who would learn to fly one day must first learn to stand and walk and run and climb and dance; *one cannot fly into flying*.

——Friedrich Nietzsche

The evaluation of benefit and risk of devices in a given type of patient, cardiac or otherwise, is made more complex in that the results may well depend on the technique applied and accompanying pharmacologic therapies used.

Interventional cardiology is replete with examples: directional coronary atherectomy never survived the results of the CAVEAT I trial in which the device was used somewhat cautiously (1), despite the much better results of the subsequent BOAT trial in which the technique was more aggressive (2) (nor did it help the device that stenting was developed nearly simultaneously). Stenting itself perhaps was saved by the recognition that low pressure implantation guided by angiography alone left many stents malapposed to the vessel wall and at risk of thrombosis (3), and by the understanding that most stent thrombosis was platelet rather than thrombin-based, hence DAPT would be better than Coumadin to prevent this complication that initially occurred in as many as 4–10% of patients (4).

There then ensues a Catch-22. In order to assess the impact of technique on relatively rare adverse outcomes, one has to vary the technique and examine outcomes in large numbers of patients. Yet to treat large numbers of patients, the FDA and other regulatory bodies generally require preliminary data showing device safety. The temptation for industry is therefore to perform initial studies in low risk patients, often from which there is only modest knowledge to gain.

So embarked the study of the Absorb bioresorbable vascular scaffold (BVS), intended to attenuate the late adverse outcomes associated with DES, ascribed to the permanent irritant effect of the stent. Of the three physical attributes of this BVS that would eventually be understood to impact outcome, only one was focused upon in the early experience—that oversizing the device by >0.5 mm would cause it to tear along its backbone and lose all its radial strength. Concern about this fragility led to the initial admonition to implant it gingerly—generally at low-medium pressure and not to post-dilate it forcefully, as is now the recommended technique. When used in the simple population of patients and lesions in the ABSORB B series, this approach worked well (5). Further experience in more complex situations (e.g., GHOST-EU) (6) showed the limitations of the BVS so used—thrombosis at 2–4× the expected rate in the first year. It became apparent that between the device strut's considerable height (157 μm, twice that of a contemporary DES) and strut width (impairing embedding into the vessel wall), that much more blood turbulence distal to each strut was created compared to a DES, making the device quite thrombogenic (7).

Unfortunately, as focus of the early studies of BVS was not on the interaction of device and technique, and scaffold thromboses were relatively rare, lessons were learned slowly. Credit should go in particular to Puricel and colleagues for studying this issue and imparting suggestions for its remedy (8).

By the time the current PSP technique was codified and promulgated, many large scale randomized comparisons of

BVS *vs.* contemporary DES were underway or completed—notably the ABSORB II and III trials, as well as the AIDA trial (the focus of these remarks) (9). As used today, PSP stands for predilation at a 1:1 ratio to reference vessel size, use in appropriately sized vessels (2.5–3.75 mm, assessed visually) and post-dilatation with an oversized balloon (1.10–1.24:1 *vs.* scaffold size) at high pressures [≥16–18 ATM (there is still debate about the details for this)]. Post-hoc analyses suggest that use of this approach can reduce risk of 1 year scaffold thrombosis by a relative 50–70%, likely but not yet prospectively proven, to lower the risk into the range seen with DES (8,10).

The AIDA trial was designed to compare results with BVS to that of XIENCE metallic everolimus-eluting stent for patients typical for "routine clinical practice", using a non-inferiority design and a primary endpoint of target vessel failure at 2 years (non-inferiority margin of 3.3%, 90% power with 2,690 patients) (11), later modified to a margin of 4.5% and 1,845 patients (9). Exclusion criteria were rare, including bifurcations, vessels of diameter <2.5 or >4.0 mm, those requiring >70 mm of stent or scaffold and in-stent restenosis. Lesions were to be predilated with a balloon undersized to the vessel by 0.5 mm yielding a stenosis <40%, and a post-dilatation strategy was not initially prescribed (it was recommended beginning October 2014). Intravascular imaging (IVUS or OCT) was optional. DAPT was mandated for at least 1 year. The first patient was enrolled in August 2013.

Nineteen percent of DES-receiving patients were enrolled, and it is not yet clear how these patients were reflective of the total practice cohort. Baseline characteristics were well matched between the two randomized groups, and were notable for QCA-determined reference vessel size of 2.67 mm and mean scaffold length of 20 mm. 19% of Absorb patients had vessels smaller than intended per protocol. In the Absorb group, post-dilatation was performed in 74% of patients, at an average balloon: scaffold ratio of 1.07 and pressure of 15.4 ATM. Final diameter stenosis was 17%±9.5% (9% had stenosis ≥30%).

The primary endpoint occurred in 11.8% of Absorb patients and 10.8% of XIENCE patients at 2 years by KM estimate [P= for non-inferiority not given, as this was a data and monitoring safety board (DSMB) requested non-final result]. Somewhat disturbingly and prompting the DSMB to act, definite or probable device thrombosis occurred in 3.5% of Absorb and 0.9% of XIENCE patients (P<0.001). Interaction testing found no significant correlates of Absorb thrombosis. On the basis of these findings, the DSMB recommended prolonged DAPT for the Absorb patients and early publication of the results.

What do the results of AIDA tell us? In retrospect, it's easy to be critical, 19% of patients had vessels too small for study entry and both pre-dilatation and post-dilatation were not performed by contemporary standards, but it should be acknowledged that the Amsterdam group designing the AIDA trial had only what came before them to work from. The results are certainly concordant with those of studies using similar technique [e.g., ABSORB III (12)] and do not quell the concern raised about scaffold thrombosis in the first 3 years after implantation raised now by several studies. The results of the ABSORB IV trial will prospectively test the importance of better vessel sizing (only 4% too small) and post-dilatation. By the time this article goes to press, the 30 day results should have been presented. Until more reassuring data are available, and given the generally excellent short and mid-term results using 2nd generation DES, the Absorb scaffold should be used very judiciously and patients who have already received it should be carefully vetted for prolonged (3 years) DAPT. That said, preliminary pooled data from ABSORB IV look decidedly better than those from ABSORB III, and maybe after seeing those results we'll be running and dancing.

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Footnote

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