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What lessons can be learned from the experience with bioresorbable scaffolds to date?

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Recently I was invited to give a lecture at the Cardiovascular Revascularization Therapeutics meeting outside Washington DC. The title I was asked to talk on was, "What needs to be done to update the ESC guidelines on bioresorbable scaffolds?". At present these guidelines give a class III recommendation for the use of scaffolds outside the setting of clinical studies[1]. This is based on the fact that at the time of writing only one approved scaffold had randomised trial data available and that these data showed a clinical performance inferior to standard drug-eluting stents, at least at medium-term follow-up. The other scaffolds with CE mark did not have any randomised trial data available at all. Preparing for the talk, it seemed that the most relevant question was, "What lessons have we learnt from the experience with bioresorbable scaffolds to date, and with the Absorb bioresorbable vascular scaffold experience in particular?". With the aid of the retrospectoscope a number of lessons seem to be important.

#1. Non-clinical testing must be further refined in order to have greater translation relevance

Reviewing the animal studies with Absorb retrospectively, the main message seems to be that the studies were not particularly helpful in predicting the problems that later emerged with this technology. The main conclusion from the studies was that the safety of the Absorb scaffold seemed to be similar to conventional stents, both at early and late follow-up[2]. Studies also showed that expansile remodelling appeared to be characteristic of the healing response with the Absorb scaffold. Finally, non-clinical investigations suggested that resorption was considered complete at 36 months. We now know that none of these three observations translated into clinical practice.

It is a generally accepted fact that non-clinical studies are intended to give insight into safety and that limited information can be gleaned regarding efficacy[3]. The non-clinical trials with Absorb failed to anticipate problems related to acute device thrombosis, as well as long-term issues related to scaffold dismantling. There is a wide variety of reasons for this but one of them is that typically non-diseased animal models are used. Such models don't give any pointers to how the scaffold will behave in disease situations – for example, in fibrotic or calcified lesions. Interestingly, however, looking back at the detail of one of the reports, one finds the first hints of potential problems with scaffold discontinuity[2]. Towards the end of the results section, investigators reported that discontinuities of scaffolds were observed in two animals, findings that could not be easily explained. Indeed, the investigators

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commented that "Although not specifically known, the inflation rates used during implantation of these scaffolds may have exceeded those detailed in the instructions for use for Absorb…". In fact, it was the first sign of a problem that ultimately resulted in the withdrawal of the technology from the market.

#2. Single-arm clinical trials failed to identify problems with the technology

A number of single-arm clinical investigations with the Absorb scaffold were published and analysed in detail. The two initial clinical investigations, ABSORB Cohort A and ABSORB Cohort B, enrolled 30 and 101 patients, respectively. Results at early follow-up seemed encouraging with low rates of adverse cardiac events. Subgroups of patients with surveillance imaging also showed results supportive of positive remodelling. Follow-up was carried out up to five years and data appeared to show sustained safety[4,5].

Both these studies suggested good clinical performance, but the obvious limitation is lack of a comparator arm. This means that the impact of patient selection cannot be well assessed. This is likely a more critical limitation than the small size of the trials. Indeed, although they were modest in size, random treatment allocation in the ABSORB II and ABSORB Japan trials allowed identification of possible differential clinical safety compared with conventional stents[6,7].

#3. The time point of primary hypothesis testing is a critical component of trial design

Looking back now, it is somewhat difficult to remember that safety at 12 months was thought to be the important landmark to reach with bioresorbable scaffolds. Many experts were confident that, if the difference in performance against standard stents at 12 months was not too great, the superior performance of the scaffold beyond 12 months would translate into clear clinical advantage. There was no broad appreciation that late outcomes could be worse with the investigational device[8]. Indeed, the pivotal ABSORB III trial was designed with primary hypothesis testing at 12 months. Accordingly, analysis at 12 months was somewhat misleading[9], and it was only during two- to three-year follow-up that clear differences between the devices became obvious[10]. This highlights the importance of assessing clinical outcomes at or after the time of complete resorption of the scaffold.

#4. Investigator-initiated trials may provide important information in addition to industry-sponsored trials

The importance of large-scale trials with new technologies that are investigator-initiated was also an important lesson. Indeed, this applies not just to the field of scaffold technologies or coronary devices, as Pocock and Gersh have highlighted[11]. For a number of reasons, the AIDA trial was an important clinical investigation. Not only was it large in scale but, more importantly, by being less selective in patient enrolment, it had greater external validity. All clinical trials involve some degree of patient selection – both implicit and explicit – but this can be reduced by the use of studies with broad inclusion criteria that are conducted according to practices similar to those used in the real world. Indeed, the model of registry-based randomised trials has many of the desired features of clinical investigations with high relevance for evaluation of medical devices in general and coronary stents in particular. It is important that funding agencies recognise the value of such trials in the landscape of clinical investigations and make financing available to conduct these types of trials.

#5. Consecutive patient, post-market surveillance registries provide critical insight into device safety

For the reasons already discussed above, single-arm studies provide limited information in relation to comparative efficacy. Nevertheless, enrolment of consecutive patients with newly approved high-risk medical devices into prospective clinical registries can provide insight into the performance of these devices in the real-world setting. Possible gaps between performance in the setting of well controlled clinical trials and general clinical practice can be identified. In the case of Absorb, a number of clinical registries acted as the canary in the coal mine and identified potential issues regarding higher incidence of device thrombosis[12,13]. Nevertheless, it is worth noting that, although it is estimated that more than 100,000 scaffolds were implanted worldwide, only a minority had patient outcomes followed in the setting of clinical registries. The Medical Device Regulation 745/2017 that comes into force in May 2020 places increased emphasis on the full lifecycle evaluation of medical devices and requires higher degrees of post-approval clinical follow-up[14]. Although much uncertainty has been introduced by these new regulations, most observers would appreciate that older regulatory processes were somewhat outdated and, in certain cases, exposed patients to risk[15].

Conclusion

The landscape of medical device evaluation is complex and multifaceted. It is clear that the overall clinical performance of new devices such as scaffolds requires review of evidence from multiple sources. Non-clinical testing will continue to have an important role in the evaluation of novel coronary devices. However, refinements in protocols must be considered, and increased use of studies incorporating diseased animal models should be advocated. First human use studies will continue to have an important role but randomisation should be built into clinical evaluations at an early stage. Pivotal trials, which are by their nature industry sponsored, should be supplemented by investigator-led trials with broader inclusion criteria and greater generalisability. Indeed, the model of registry-based randomised trials ticks many of the boxes in relation to the desired features of clinical investigations. This should focus our attention anew on the importance of setting up and maintaining dedicated, consecutive patient, national registries, which are an important foundation stone for such trials.

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Corrigendum

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Corrigendum to: Predictors of haemodynamic structural valve deterioration following transcatheter aortic valve implantation with latest generation balloon-expandable valves

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The authors wish to apologise for the following error:

"OAC" has been changed throughout to "absence of OAC".

"Cox proportional hazards analysis revealed the following independent predictors of haemodynamic SVD during follow up after TAVI: use of a 20 mm valve (hazard ratio [HR] 9.43; p<0.001), valve-in-valve procedure (HR 9.92; p,0.001 and OAC (HR 0.46; p=0.003)" has been changed to "Cox proportional hazards analysis revealed that use of a 20 mm valve (hazard ratio [HR] 9.43; p<0.001) and valve-in-valve procedure (HR 9.92; p<0.001) were independent predictors of haemodynamic SVD during follow-up after TAVI, whereas OAC (HR 0.46; p=0.003) was a protective factor of haemodynamic SVD." [p1235]

"Our analysis revealed that OAC is significantly associated with both haemodynamic SVD and death after TAVI" has been changed to "Our analysis revealed that OAC is a significant protective factor of haemodynamic SVD after TAVI, whereas it is a predictor of death after TAVI." [p1236]

This has now been corrected online.