Bioresorbable coronary scaffolds: a novel device-based solution in search of its clinical need

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This editorial refers to ‘Bioresorbable scaffolds: rationale, current status, challenges, and future’†, by J. Iqbal et al., on page 765, ‘Bioresorbable vascular scaffolds in acute ST-segment elevation myocardial infarction: a prospective multicentre study ‘PRAGUE 19’‡, by V Kočka et al., on page 787, and ‘Everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with ST-segment elevation myocardial infarction. BVS STEMIFirst Study’§, by R. Dilettet et al., on page 777.

In this focused issue of the European Heart Journal, Iqbal et al. provide a comprehensive and thoughtful review of lessons learned from relevant pre-clinical and early clinical evaluations of bioresorbable coronary scaffolds, concentrating on the one brand (everolimus-eluting Absorb device, BVS, Abbott Vascular) that has undergone the largest and most detailed investigations thus far.† These cumulative observations were performed in small selected series, but have built up confidence in the clinical performance of BVS following extensive, carefully reported, and sequential (up to 3 years) multimodality interrogations using multislice coronary computed tomography imaging, invasive coronary angiography and its quantitation, intravascular ultrasound and tissue backscatter analysis, optical coherence tomography imaging (OCT), and coronary vasomotor testing.‡ During EuroPCR 2013, the annual congress of the European Association of Percutaneous Cardiovascular Intervention, the community was asked to identify the hot topic of the moment and, by far, colleagues have nominated the question of the clinical usefulness of bioresorbable coronary scaffolds as the most debated issue in the field. While the results of the first randomized trial are expected at the end of 2014 (Table 1), adoption of BVS by physicians and patients has anticipated by a long way the available evidence, at least in areas with a favourable regulatory environment.

Why bioresorbable devices should and will eventually replace permanent metal stents

Percutaneous coronary revascularization strategies have improved through a continuous hurdle race that required parallel technological improvements, refinement of procedural techniques, and understanding of drug—device interactions. Metal stents were first introduced to address the many drawbacks of the plain old balloon angioplasty procedure, i.e. acute vessel recoil, flow-limiting dissection, insufficient coronary luminal enlargement, and poor predictability of the procedural outcomes.§ The first-generation drug-eluting stents (DES) were mainly proposed to address the high restenosis rates observed with the use of bare metal stents.¶ Second- and third-generation DES have been developed to address the risk of (very) late stent thrombosis.¶ Each step forward was in response to pressing clinical needs that were addressed, time after time, with novel creative solutions. The latest generation DES have demonstrated excellent results in terms of both safety and efficacy compared with the earlier generations.¶ Through the combined effect of many factors—optimized implantation techniques, careful attention to adjunctive therapy using more potent drugs, and improved blood and tissue compatibility of newer devices—the risk of stent thrombosis is presently very low, even lower than observed in the bare metal stent era.¶ Device-mandated duration of dual antiplatelet treatment can possibly be reduced to 3 months without harm after implantation of a DES using biocompatible or bioresorbable polymers.¶ In other words, it seems that the results of current generation DES can hardly be bettered by another improvement of any of its individual components (stent platform, polymer, or drug).

Why then, do so many think that bioresorbable coronary scaffolds should and will eventually replace permanent metal stent implants?

From the industry perspective, the incremental benefit from non-disruptive device improvements becomes smaller, technically increasingly challenging to deliver, and more difficult to establish at higher value with payers. Since the absolute event rates are low, large (expensive) trials are needed.¶ Eventually, even with positive trial results, their relevance is jeopardized by device obsolescence. The residual target population to be treated with the next-generation devices is presently very low, even lower than observed in the bare metal stent era.¶ Device-mandated duration of dual antiplatelet treatment can possibly be reduced to 3 months without harm after implantation of a DES using biocompatible or bioresorbable polymers.¶ In other words, it seems that the results of current generation DES can hardly be bettered by another improvement of any of its individual components (stent platform, polymer, or drug).
device is therapy resistant and becomes smaller at each step. Options for favourable reimbursement are shrinking as the perceived value of the new technology decreases, with the availability of low-cost ‘me-too’ products. Thus the return on investment is not favourable and the next technological advancement may no longer be affordable, leading to deliberate industry dis-investment in DES.

In addition to these business or financial considerations, there is increasing concern, also with the public, about the expansion of device-based therapies in all fields of medicine. Today devices are contributing to the care of multiple disorders and targeting multiple organs, whereas they were initially restricted to surgical indications, such as replacement therapy (e.g. hip prostheses or heart valves). There is increasing concern about late side effects or disease substitution, all potentially associated with critical liability issues (e.g. the recent scandal in France regarding failing breast implants). Lastly, appropriate concerns regarding disruption of nature by the ever escalating number of permanent implants result in growing demands for the future for better device biocompatibility, allowance for normal physiology and regular care, including imaging, and ultimately predominance use of fully bioresorbable materials.

Thus industry and society will favour bioresorbable coronary scaffolds, even when their performance is only non-inferior to current metal DES. These promises may be fulfilled with the use of BVS, pending an adequate procedural technique, namely sufficient stenosis dilation prior to implantation to allow proper device expansion. Both BVS and magnesium-based scaffolds have good radial strength and low recoil; however, a trend toward acute recoil of polymeric BVS has been reported. After that, the scaffolding provided by bioresorbable devices in the first few months after implantation is said to be equivalent to that of metal stents. Evidence for gradual and predictable bioresorption during the first 2 years after implantation has also been documented. If indeed the incremental value of bioresorbable scaffolds over durable metal stents stems primarily from their gradual disappearance, it follows that clinically relevant benefit will only become apparent after long-term follow-up of large patient groups. This will require demonstration of a significant reduction in the low (single-digit) rates of (very) late DES failure beyond 2–3 years after implantation.

Why bioresorbable devices may eventually provide superior outcomes

Proponents of this technology have promoted a number of unique features of BVS that may portend superiority over metal stents in specific patient or lesions subsets. As opposed to permanent implantation of metallic cages, BVS virtually allows preservation of the vascular geometry and physiology, including vasomotion. Together with deposition of a uniform fibrous neointimal layer and potential late lumen enlargement, these devices may be appealing for use in patients with vulnerable plaques. Proponents have suggested that preservation of the vascular architecture may facilitate clinical success in vulnerable plaques.

Table 1 Ongoing and planned randomized clinical trials on bioresorbable vascular scaffolds

<table>
<thead>
<tr>
<th>BVS</th>
<th>Study</th>
<th>Target patients</th>
<th>No. of patients</th>
<th>Endpoints</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorb</td>
<td>Absorb II</td>
<td>Ischaemic heart disease</td>
<td>501</td>
<td>Vasomotion and LLL at 2 years</td>
<td>2:1; superiority vs. vasomotion; non-inferiority vs. LLL</td>
</tr>
<tr>
<td></td>
<td>Absorb III</td>
<td>Ischaemic heart disease</td>
<td>2250</td>
<td>TLF at 1 year</td>
<td>2:1; non-inferiority</td>
</tr>
<tr>
<td></td>
<td>Absorb Japan</td>
<td>Ischaemic heart disease</td>
<td>400</td>
<td>TLF at 1 year</td>
<td>2:1; non-inferiority</td>
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<tr>
<td></td>
<td>Absorb China</td>
<td>Ischaemic heart disease</td>
<td>440</td>
<td>LLL at 1 year</td>
<td>2:1; non-inferiority</td>
</tr>
<tr>
<td></td>
<td>AIDA</td>
<td>All comers</td>
<td>2670</td>
<td>TVF at 2 years</td>
<td>1:1; non-inferiority</td>
</tr>
<tr>
<td></td>
<td>ISAR-ABSORB-MI</td>
<td>STEMI</td>
<td>260</td>
<td>%DS at 6–8 months</td>
<td>1:1; non-inferiority</td>
</tr>
<tr>
<td></td>
<td>TROFI II</td>
<td>STEMI</td>
<td>190</td>
<td>Healing score at 6 months</td>
<td>1:1; non-inferiority</td>
</tr>
<tr>
<td></td>
<td>Absorb IV</td>
<td>Ischaemic heart disease</td>
<td>3000</td>
<td>Patient-reported angina at 1 year; TLF at 1–5 years</td>
<td>1:1; non-inferiority</td>
</tr>
</tbody>
</table>

BVS, bioresorbable vascular scaffold; %DS, percentage diameter stenosis; LLL, late lumen loss; STEMI, ST-segment elevation myocardial infarction; TLF, target lesion failure; TVF, target vessel failure. Results of Absorb II are to be announced by the end of 2014. Absorb III, Absorb Japan, Absorb China, and AIDA are recruiting. The novolimus-eluting DESolve scaffold (Elixir) was granted a CE mark in May 2013; to the author’s knowledge, plans for randomized trials have not been released.
(i) coronary artery disease in patients with diabetes;
(ii) diffuse atherosclerotic involvement of epicardial vessels;
(iii) extensive multivessel disease (higher tertile of Syntax score);
(iv) PCI for ST-segment myocardial infarction (STEMI) and NSTEMI, especially in the case of high thrombus burden in large vessels;
(v) residual risk related to non-culprit lesions in patients with acute coronary syndromes;
(vi) sudden ischaemic cardiac death;
(vii) treatment of complex bifurcation stenoses;
(viii) intervention for chronic coronary occlusion with the use of simpler, safer, and less expensive tools and techniques.

It is naïve to believe that simply replacing one device by another will address all these unmet needs. Most probably, many advances will result from strategies that exacerbate synergies between pharmacological agents and devices, while other patient or lesion subsets may benefit directly from treatment with BVS, rather than DES. In fact, since BVS has become more widely available for clinical use, the feasibility of its use has been investigated in several of the above-mentioned potential indications.

Biodegradable vascular scaffold, a novel device-based solution for patients with ST-elevation myocardial infarction and acute coronary syndromes?

In this issue of the Journal, Kočka et al.12 and Diletti et al.13 provide the results of two observational studies designed to investigate BVS in patients with STEMI. Previous studies have been reported on smaller series or mixed populations with STEMI and other acute coronary syndromes.14–16 Altogether we now have data on 179 STEMI patients implanted with BVS. What is the message to take home from these early experiences? First, BVS implantation was feasible with 100% success rate in selected patients with STEMI, representing 20–30% of all STEMI patients treated at both institutions.12,13 Given the strict inclusion criteria of these early studies, one cannot recommend using BVS in all comers. Secondly, no specific safety concerns have been reported up to 1 month follow-up, when compared with the everolimus-eluting DES.

More interesting are the lessons learned with respect to procedural technique and invasive imaging. Similar to other clinical and angiographic settings, the intention-to-implant BVS in a STEMI patient requires extensive vessel preparation. Thrombus aspiration was performed more often than in the comparator group treated with DES (40% vs. 10%).12 Lesion pre-dilatation was almost uniformly applied, with very low rates of direct stenting. These specific features of the procedural technique are justified by the fact that BVS are bulkier than metal stents. Vessel patency and optimal lumen expansion prior to scaffold delivery are essential, keeping in mind that BVS scaffolds are less amenable to aggressive post-dilatation because of the risk of polymeric strut fracture. Precise estimation of the vessel size is crucial to allow appropriate selection of the scaffold size, which is inherently challenging in STEMI patients due to vasoconstriction, slow flow, and residual thrombus load. To overcome the limitations of coronary angiography in the correct estimation of true vessel size and avoid scaffold fracture, the PRAGUE-19 study group performed a systematic oversizing of BVS. This strategy was associated with a 30% higher risk of edge dissections reported to be clinically silent in most of the cases.12 By embracing this strategy, one has to keep in mind the possibility that additional BVS implantation will be triggered by flow-limiting edge dissections. In the majority of cases, this will lead to scaffold overlap and result in 0.30 mm circumferential scaffold thickness, possibly interfering with local rheology and raising concerns regarding pro-thrombotic effects. These issues illustrate the limitations of currently available scaffolds and how their use forces operators to deviate from today’s state of the art interventional practice. Only randomized evaluations will solve the trade-off between early procedural disadvantages and (very) late patient benefit.

Another downside of the more extensive vessel preparation that is required for BVS implantation is that this might result in higher risk of distal embolization and no-reflow, even before scaffold implantation. On the other hand, one may hypothesize that BVS implantation will reduce the risk of no-reflow as a consequence of the “snow racket concept.”13 Due to the thicker struts (150 μm) and larger wall surface coverage, BVS might entrap more thrombotic material between the scaffold and the vessel wall than the current thin strut DES, therefore reducing the risk of squeezing the thrombus and debris through the struts (Figure 1). The limited sample size of the present studies does not allow any conclusion to be drawn on this matter, yet the reported facts are of interest: (i) no-reflow was low at 2–3%; and (ii) glycoprotein IIb–IIIa inhibitors were given in 30% of cases (whether electively or for bail-out is not specified). This latter rate was three times their use in patients implanted with metal stents.13,15

Cases of early scaffold thrombosis have been reported in these early experiments.12,15 One scaffold thrombosis occurred after 13 days in a patient in whom dual antiplatelet therapy was withdrawn 3 days after the acute event. Of note, edge-to-edge implantation of two BVS had been performed with a 2 mm gap in between, as shown by OCT. Gori et al.15 reported four scaffold thromboses (three definite, one probable). OCT showed suboptimal scaffold expansion as the most commonly associated observation. Patients were managed with thrombus aspiration and/or balloon dilatation, without additional scaffolding. Whether implantation of a metal DES can be useful is not known. All patients experiencing scaffold thrombosis were treated with ticagrelor. At this time, it is not known whether one antiplatelet agent should be preferred, or for how long they should be prescribed. Most importantly, no long-term data are available yet. It can be hypothesized that possible late adverse events associated with acquired malapposition will be addressed by bioresorption of the scaffold (Figure 1). Indeed, late malapposition with permanent metal stents can occur after dissolution of the thrombus initially trapped behind the stent struts.

Summary

The currently available data are limited, we know that BVS can be implanted in selected STEMI patients. Whether this will be beneficial remains to be demonstrated by medium- and long-term follow-up. Provided observational studies continue to be associated with neutral or positive safety and efficacy signals, randomized evaluations will be required to demonstrate eventually that BVS represents a
novel device-based solution for patients with STEMI and acute coronary syndromes. As of today, the same conclusion applies to every other potential patient or lesion subset that may potentially benefit from temporary scaffolding, beyond the expected benefits of newer generation DES. Demonstrating the evidence of non-inferiority will hardly be feasible. As the technical features of next-generation scaffolds improve, they may gradually replace metal stents. Over the next 5–10 years, we will probably witness another natural ‘evolution’ in the development of coronary devices, with them eventually becoming temporary, rather than durable implants. Yet, in order to fulfil the promises of a disruptive technology, scaffolds will have to demonstrate their superiority in treating clinical conditions that do not respond well enough to current interventional approaches. A therapeutic ‘revolution’ stems from the evidence that a novel device-based solution addresses a pressing clinical need, not from the elusive quest for a clinical application for a new technology.

Acknowledgments

The authors would like to acknowledge the vision, critical guidance, and enthusiastic inspiration of Professor P.W. Serruys in nurturing the development of this novel technology.

Conflict of interest: Institutional research grants from pharmaceutical and device (Abbott Vascular, Biotronik) companies. Honoraria and fees on behalf of E.B. and W.W. go to the Cardiovascular Research Center Aalst. W.W. is co-founder and shareholder of Argonauts, Genae and Cardio³BioSciences.
A patient with chest pain during dobutamine stress echocardiography

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A 57-year-old male without any significant past medical history is admitted to the intensive care unit for a suspicion of acute coronary syndrome. He is a non-smoker and mentioned a mild hypercholesterolaemia. He reports an


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References