Bioresorbable Scaffolds for the Management of Coronary Bifurcation Lesions

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ABSTRACT

The use of bioresorbable scaffolds (BRS) may be associated with benefits including restoration of endothelial function, positive vessel remodeling, and reduced risk for very late (stent) thrombosis compared with metallic stents by virtue of their complete absorption within 3 to 4 years of implantation. When treating bifurcation lesions, these advantages may be even more pronounced. The aim of this review is to summarize current experiences and technical considerations of bifurcation treatment with BRS. Because of the physical properties of current-generation BRS, there are concerns with regard to the efficacy and safety of this novel technology for the treatment of bifurcations, with the potential for increased rates of scaffold thrombosis and side-branch occlusions, and as a consequence, bifurcations have been excluded from the major BRS trials. Nevertheless, BRS have been used for this indication in clinical practice, as evidenced by “real-world” registries. Considering the potential limitations, specific technical considerations and modified bifurcation strategies should be used in an attempt to attenuate problems and achieve optimal procedural and clinical outcomes. (J Am Coll Cardiol Intv 2016;9:989-1000) © 2016 by the American College of Cardiology Foundation.

Technological and procedural advances in recent years have resulted in vastly improved clinical outcomes following percutaneous coronary intervention. In particular, the advent of current-generation drug-eluting stents (DES) reduced the rate of restenosis compared to bare-metal stents (1,2). Although the treatment of complex lesions with metallic DES is now well established (3), coronary bifurcation lesions remain a technical challenge, even with contemporary metallic stents, because of higher rates of increased restenosis (4,5) and stent thrombosis (6), which are likely due to incomplete neointimal coverage and permanent metallic caging of the flow divider and the side branch (SB).

The use of bioresorbable scaffolds (BRS) for the treatment of coronary artery disease is potentially advantageous by virtue of complete bioabsorption of struts, which may result in the recovery of vasomotor function, preserved possibility for positive remodeling, and a potential reduction of very late clinical adverse events because of the absence of a residual permanent foreign body (7). These potential advantages may be even more pronounced in the setting of bifurcation lesions, which are associated with a greater occurrence of adverse events compared with “simple” lesions. However, clinical experience with this novel technology for bifurcation lesions is limited, and there is currently no consensus or recommendation with regard to the optimal technical approach.

Our aim in this review is to summarize current experiences and technical considerations of bifurcation treatment with BRS.
SPECIFIC CONSIDERATIONS FOR BRS TREATMENT OF BIFURCATIONS

A number of randomized trials and retrospective studies with metallic stents demonstrated that when possible, a single stent (provisional strategy) is superior to the implantation of stents in both branches of the bifurcation (4,5,8,9). If the bifurcation lesion is not suitable (e.g., because of significant SB disease or the presence of dissection), an elective 2-stent strategy should be adopted with accepted techniques, including mini-crush, DK-crush, T-stenting, and culotte stenting (9). However, these techniques cannot be simply performed with BRS in a similar fashion to DES without taking into account the important differences in physical properties between the 2 platforms. As a consequence, when a BRS is being considered for the treatment of a bifurcation lesion, operators should consider the following: 1) fragility; 2) overexpansion limit; 3) strut thickness and width; and 4) deliverability and crossability.

Specific procedures such as SB ballooning, the proximal optimization technique (POT), or kissing balloon inflation (KBI) used for bifurcation lesions should therefore be modified. Operators should pay careful attention to each step when further optimization of the SB is deemed necessary following BRS implantation to the main branch (MB).

The greater strut thickness (~150 μm) and width of the current BRS (Absorb, Abbott Vascular, Santa Clara, California) compared with DES are important procedural considerations. Strut thickness and malapposition are considered critical factors in modulating thrombogenicity in the setting of metallic stents (10). Therefore, techniques that minimize strut overlapping and protrusion into the vessel cavity should be used to reduce the risk for scaffold thrombosis. Furthermore, the relatively bulky mass of BRS results in a larger device profile compared with the Xience everolimus-eluting stents (Abbott Vascular) (Absorb 1.43 ± 0.02 mm vs. Xience 1.14 ± 0.01 mm; p = 0.04) (11). When a provisional 2-stent strategy (e.g., the T-stenting and small protrusion [TAP] technique) is used, operators should therefore be wary of increased difficulty in delivering a BRS, because of its size and physical properties, leading to fragility. Similar concerns are present regarding other techniques, such as culotte and crush.

CURRENT EXPERIENCE OF BRS USE FOR THE MANAGEMENT OF CORONARY BIFURCATION LESIONS

The pivotal BRS studies to date focused solely on “simple” lesions, excluding bifurcation lesions with SB diameter larger than 2 mm (12,13). The major randomized, prospective, and retrospective BRS studies are summarized in Table 1. Currently, there are limited data reporting clinical outcomes following BRS implantation in bifurcation lesions. The prevalence of bifurcation lesions varies greatly among studies and ranges from 15% to 45% (14–21). The only study that investigated clinical outcomes at 1 year following BRS implantation in bifurcation lesions (22) reported rates of major adverse cardiac events and target lesion revascularization to be lower, as expected, in the provisional stenting group (99 lesions) compared with a planned double-stenting group (23 lesions) (major adverse cardiac events: 9.5% vs. 11.2%; p = 0.91; target lesion revascularization: 5.5% vs. 11.2%; p = 0.49; provisional stenting vs. planned double-stenting, respectively). The remaining published data regarding the 2-stent techniques (including provisional double-stenting) with BRS are currently limited to bench tests and case reports (23–26). “Real-world” registries including complex lesions (without exclusion of bifurcations) demonstrated a trend toward higher rates of scaffold thrombosis, especially in the setting of acute coronary syndromes (14,15,27–33).

INDICATION OF BRS FOR BIFURCATION LESIONS

PHYSICAL PROPERTIES OF BRS. On the basis of ex vivo bench testing, Ormiston et al. (11) demonstrated that the 3.0-mm Absorb BRS can be expanded up to 3.8 mm without strut disruption. However, there are no data available supporting these observations in vivo, and current recommendations suggest a maximal overexpansion of 0.5 mm beyond the nominal scaffold size (but this varies among different BRS platforms). We therefore recommend the judicious use of quantitative coronary angiography or baseline intravascular imaging such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) to determine the suitability of BRS for a bifurcation lesion.

LESION SELECTION. In view of the physical properties and limitations of current-generation BRS, not all bifurcation lesions are amenable to treatment with this technology. Specifically, we do not recommend BRS for the treatment of bifurcations with a >0.5-mm size discrepancy between the proximal and distal MB,
which would require post-dilation of the proximal segment beyond the expansion limit, resulting in risk for strut disruption.

The smallest diameter currently available Absorb BRS is 2.5 mm, and therefore we do not recommend its use in MBs smaller than this. Finally, bifurcations that are best treated with a 2-stent strategy should be treated only with a BRS in the SB (in addition to the MB) if the anatomy is favorable for T stenting and the size of the SB is clearly 2.5 mm or greater; if this is not the case, we recommend a “hybrid” approach with a metallic DES in the SB and a BRS in the MB.

### TECHNICAL CONSIDERATIONS OF BRS IMPLANTATION IN BIFURCATION LESIONS

**PROVISIONAL APPROACH REMAINS THE DEFAULT STRATEGY.** Even though the optimal strategy for the treatment of coronary bifurcation lesions with metallic stents is still the subject of ongoing research, the current consensus supports a provisional stenting strategy if possible (9). However, up to 30% of patients who are initially treated with metallic stents using a provisional strategy require crossover and the implantation of a second stent (4,5,8). Although some case reports and bench-test models have shown...
successful short-term results of planned 2-stent strategies (14,22,34), even when implanting BRS, the provisional approach should be the default strategy for the majority of bifurcation lesions (Figure 1). However, because of the physical properties of current-generation BRS, there are some specific considerations (e.g., modified bifurcation techniques for crossover) that need to be taken into account with regard to the management of the SB: 1) SB occlusion; 2) strut disruption following SB ballooning or KBI; and 3) strut protrusion into the MB (Central Illustration).

**SB Occlusion and Periprocedural Myocardial Infarction.** Acute SB occlusion following BRS implantation in the MB is an important concern because of the thicker (157 μm) and wider (2.5- and 3.0-mm Absorb BRS, 190.5 μm; 3.5-mm Absorb BRS, 215.9 μm) struts compared with current second-generation DES. In the ABSORB EXTEND (A Continuation in the Clinical Evaluation of the ABSORB Bioreosorbable Vascular Scaffold [BVS] System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) substudy, Muramatsu et al. (35) reported that BRS implantation was associated with a higher incidence of SB occlusion (especially small SBs) compared with everolimus-eluting metallic stents in the SPIRIT (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions) trials (Absorb BRS 6.0% vs. Xience DES 4.1%; p = 0.09). In contrast, the opposite trend was observed in the ABSORB II (A Clinical Evaluation to Compare the Safety, Efficacy and Performance of Absorb Everolimus Eluting Bioresorbable Vascular Scaffold System Against Xience Everolimus Eluting Coronary Stent System in the Treatment of Subjects With Ischemic Heart Disease Caused by de Novo Native Coronary Artery Lesions) randomized trial (Absorb BRS 5.3% vs. Xience DES 7.6%; p = 0.07) (36).

When evaluating the incidence of periprocedural myocardial infarction (creatine kinase >2 times the upper limit of the normal), there were no significant differences between the groups (ABSORB EXTEND: 5.5% vs. 3.8%; p = 0.51; ABSORB II: 5.2% vs. 1.9%; p = 0.14; Absorb BRS vs. Xience DES, respectively).

In a propensity-matched comparison between the Absorb BRS (strut thickness 157 μm) and the first-generation sirolimus-eluting stent (Cypher; Cordis Corporation, Johnson & Johnson, Warren, New Jersey) (strut thickness 152.6 μm) (37), BRS implantation was associated with a higher incidence of periprocedural myocardial infarction (Absorb BRS 13.1% vs. Cypher 7.5%; p = 0.05). Although the incidence of SB occlusion was not evaluated in this study, abluminal strut surface area was an independent predictor of periprocedural myocardial infarction. The impact of the wider BRS struts on SB occlusion when used to treat bifurcation lesions in the presence of larger (>2 mm) SBs is currently poorly defined. However, considering these observations and concerns, operators should have a low threshold to protect the SB if large enough to be crossed with a coronary wire.

**Following BRS Stenting to MB: The POT.** The POT is considered to be invaluable in ensuring adequate stent apposition in the proximal MB and to aid in SB rewiring (9). Although it remains unclear whether the POT should be performed routinely in the context of bifurcation stenting, it is useful to facilitate SB rewiring due to the presence of bulky BRS struts straddling the ostium. As previously mentioned, the maximal overexpansion limit should be respected when performing the POT on the implanted BRS to prevent strut disruption.

**Following BRS Stenting to MB: KBI.** Currently, the advantages of routine KBI following single-crossover stenting with metallic stents have not definitively been demonstrated (38,39). However, bench testing demonstrated a distortion of BRS struts in the MB...
with resultant malapposition following SB dilation (11). In the case of SB compromise following MB stenting, SB dilation followed by MB post-dilation or KBI should be considered (9). The KBI technique after MB stenting enables restoration of the natural bifurcation anatomy and improvements of strut apposition at the ostium of the SB (40,41). In contrast, the disadvantages of KBI include over-expansion of the proximal BRS and resultant strut disruption, as well as risk for SB dissection. Therefore, when KBI is indicated, we suggest the following:

1. For provisional single-stenting (Figure 2), avoid KBI unless needed because of SB compromise. If final KBI is performed, use a mini-KBI (Figure 3, panel 3-2) without SB balloon protrusion into the main vessel (“snuggle” kissing).
2. Four provisional double-stenting (Figure 2), final mini-KBI should be performed to minimize mal-apposition of struts and deformation of the BRS in the MB.
3. For elective double-stenting (Figure 4), the first KBI should be performed after having implanted the BRS or DES in the SB and before implanting the BRS.
in the MB. The final mini-KBI following BRS stenting in the MB should be performed only if the SB ostium looks compromised.

Ormiston et al. (11), on the basis of bench-testing, reported that the safe threshold without strut fracture with a 3.0-mm Absorb BRS was 10 atm for SB dilation with a 3.0-mm noncompliant balloon. Furthermore, the safe threshold for mini-KBI for 3.0-mm Absorb BRS with 3.0-mm noncompliant balloons was 5 atm. These findings suggest that when SB ballooning or KBI is performed, gentle inflation with low pressure should be used. To minimize the damage of MB BRS, a smaller balloon for the SB can be safely used to avoid these complications.

The other concern regarding the use of BRS in bifurcation lesions is neointimal growth at the ostium of the jailed SB, which may disrupt SB flow (Figure 5), and the potential embolization of this material (the BRS strut itself and or neointimal tissue on the struts) downstream. In the initial ABSORB trial (42), the ostial area of the jailed SB was reduced because of neointimal growth at 1 year. However, the ostial area increased because of the reduction of neointima and recreation of the bifurcation carina at longer term follow-up. These findings may further support a single-crossover strategy jailing a large SB (42,43).

**PROVISIONAL STENTING OF A COMPROMISED SB.** As with metallic stents, SB stenting should be considered after a provisional approach and implantation of a scaffold in the MB, if there is impaired flow in the SB, dissection, or significant residual stenosis. If the bifurcation angle is close to 90°, provisional T stenting with implantation of a second BRS or metallic DES is appropriate. However, operators should keep in mind the potential difficulty of delivering a BRS, due to its bulky physical properties and its fragility, which may result in damage to the scaffold before implantation; therefore, we are quite reluctant to suggest BRS implantation in the SB following BRS stenting of the MB. A conventional metallic DES should be considered, which may facilitate crossing without damaging the BRS implanted in the MB.

As preferred with the use of metallic stents (44,45), the TAP technique appears to be favorable for bifurcations with a shallow angle (Figure 3). Although TAP with 2 BRS is technically possible, there are some potential limitations to this approach. First, the resultant neoplastic carina (overlapping BRS struts at the carina) may accelerate hyperplasia and thrombus formation at the carina. Second, precise stenting must be performed to prevent large scaffold protrusion into the main vessel on one hand or missing the ostium of the SB on the other. In a bench model, when provisional BRS stenting to the SB was performed in a 75° bifurcation angle, protrusion of the SB BRS into the main vessel was unnecessary (26). Therefore, careful attention should be paid when the TAP technique is used on bifurcations with angles <75°. Finally, SB rewiring should be performed through the distal end of the MB scaffold if possible. The same concerns regarding implanting a BRS on the SB outlined for the T technique apply to the TAP approach. Therefore, a conventional DES to the SB is the most suitable solution. These limitations regarding BRS implantation on the SB are likely to be overcome with the introduction of second-generation BRS with a lower profile that are more forgiving of overdilation.

**ELECTIVE DOUBLE-STENTING STRATEGY.** The current evidence for the elective double-stenting strategy using BRS has been limited to case reports (23-25,43,46) and ex vivo bench tests (26). In a small study (23 lesions) investigating clinical outcomes following elective double-stenting with BRS, the rate of target lesion revascularization at 1 year was 11% (22). However, because of the small group of patients, patency rates of each specific 2-stent technique were not available.

In common with the technical aspects of provisional stenting, meticulous procedural techniques...
that minimize strut protrusion into the MB should be used to optimize clinical outcomes. Therefore, we suggest that when considering the use of 2 BRS for the treatment of a bifurcation lesion, the following points should be borne in mind:

1. Use 2 BRS only if the SB is 2.5 mm or larger.
2. When the anatomy allows simple T stenting, final mini-KBI should not be performed routinely and only if the SB ostium looks compromised following MB stenting.
3. Avoid culotte and mini-crush stenting with 2 BRS, because of the risk for strut fracture and excessive overlap of the BRS.

To avoid overlapping BRS struts, metallic DES can be considered for the elective treatment of the SB (Figure 4). When treating bifurcation lesions with a wide angle (>70°), T stenting would be the preferred technique to avoid overlapping scaffolds at the carina (26) and, if necessary, with minimal protrusion into the carina (modified T stenting) (Figure 6). The other possible technique that should be considered is a hybrid mini-crush technique (BRS for the MB and metallic DES for the SB) (Figure 7) (22,43), a technique that can be broadly used for any bifurcation angle (47,48). This hybrid strategy is particularly useful for bifurcation lesions with narrow angles. In cases of an elective double-stenting strategy, the first KBI (after SB stenting) should be mandatory to reduce strut protrusion and jailing struts at the orifice of the SB (48,49).

**SCAFFOLD OPTIMIZATION AND EFFECTIVE ANTI-THROMBOTIC THERAPY ARE ESSENTIAL.** With the use of metallic stents, adequate stent expansion and apposition confirmed by IVUS resulted in significant

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**FIGURE 3  A Representative Case Treated With T-Stenting and Small Protrusion Technique**

1. Baseline angiogram revealing a true bifurcation lesion of the left anterior descending coronary artery (LAD).
2. The ostium of the SB was compromised (Thrombolysis In Myocardial Infarction flow grade 2) following BRS stenting to the main branch (MB).
3. The proximal optimization technique (POT) was performed with a 3.5-mm noncompliant balloon.
4. First kissing balloon inflation (KBI) was performed with 3.0-mm (MB) and 2.5-mm (SB) BRS.
5. Angiogram following KBI shows residual stenosis at the ostium of the SB.
6. A second 3.0 × 12 mm BRS was implanted using the T-stenting with small protrusion technique.
7. Final KBI with minimal overlapping balloons; the SB balloon is always deflated last to prevent SB crushing of the SB device.
8. Final angiogram showing an excellent result in both MB and SB.
9. Intravascular ultrasound (IVUS) demonstrated minimal overlapping struts (red arrows) in the proximal main branch.
10. Overlapping BRS struts (neoplastic carina, yellow arrows) were observed at the bifurcation site.
11. IVUS image showing well-apposed BRS struts distal to the bifurcation. Diag. = diagonal; MSA = minimal scaffold area; other abbreviations as in Figures 1 and 2.
reductions in restenosis (50,51) and stent thrombosis (52,53). It should be noted that results from registries (14) and meta-analyses (54,55) have identified a higher rate of thrombosis with BRS than would be expected for current-generation DES. It is unclear if these instances are related to procedural factors (e.g., insufficient lesion preparation, inappropriate scaffold sizing, and lack of routine post-dilation), lesion complexity (e.g., bifurcations), or the device itself. Future studies are required to further understand this finding.

Taking into account that the thick struts of BRS occupy a larger area and protrude more than current-generation DES into the vessel lumen, extrapolating these experiences, it would be reasonable to assume that the use of intravascular imaging would be beneficial in confirming and optimizing the expansion and apposition of the implanted BRS. Furthermore, more aggressive antiplatelet therapy might be beneficial, although there are currently no data evaluating the efficacy of newer antiplatelet agents (e.g., prasugrel or ticagrelor) in the context of BRS over and above clopidogrel.

In the setting of “simple” stenting such as single-crossover stenting, either IVUS or OCT would be sufficient for BRS optimization. However, in cases of

**FIGURE 4** Proposed Algorithm for the Treatment of Coronary Bifurcations With Elective 2-Scaffold/Stent Strategy

**FIGURE 5** Neointimal Bridge on the Bioresorbable Scaffold Struts Jailing the Side Branch

Meticulous procedural techniques that minimize strut protrusion into the main branch should be used to optimize results when an elective 2-scaffold/stent technique is used. The specific technique should be determined on the basis of the bifurcation angle to minimize overlapping and protruding struts into the main branch at the site of the bifurcation lesion. To avoid overlapping BRS struts, a metallic DES can be considered for treatment of the side branch. KBI = kissing balloon inflation; other abbreviations as in Figure 1.
SB intervention after BRS implantation to the MB, OCT may be preferable (to IVUS) to confirm optimal SB rewiring, which may reduce the risks for strut disruption and malapposition (56). Furthermore, in cases of complex stenting such as elective double-stenting with BRS, OCT may have additional advantages for BRS optimization because of its higher resolution (in comparison with IVUS), allowing more precise visualization of the BRS overlap site and the identification of any disrupted struts or jailed BRS struts. However, it should be noted that the clinical impact and management of strut disruption are currently unclear.

FUTURE PERSPECTIVES

Technological advances should allow the manufacture of BRS with thinner and narrower struts without the loss of radial strength. This would theoretically result in a less bulky device with improved deliverability and promote superior vascular healing, with lower thrombogenicity compared with the currently available BRS.

There are a number of BRS currently in development with different properties, including composition, bioabsorption period, and expansion limit, which may further enhance the applicability of various technical approaches to the treatment of bifurcation lesions.

CONCLUSIONS

Although bifurcations were excluded from the pivotal BRS trials, with greater operator experience, BRS are increasingly being used for the treatment of bifurcation lesions, as evidenced by published real-world registries. However, experiences with these novel devices for this indication are currently limited, and there is no consensus as to the optimal techniques when contemplating using BRS for the
treatment of bifurcation lesions. In view of the physical properties of current-generation BRS, modification of currently well-established DES bifurcation techniques should be performed to obtain optimal procedural results while avoiding strut fracture and overlap. Finally, the use of a metallic stent for the SB should be considered a very acceptable option until more forgiving scaffolds become available.

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