Coronary artery bifurcations are at an increased risk of the development of coronary atherosclerosis because of turbulent flow and low shear stress. Bifurcation lesions account for between 8% and 22% of all percutaneous coronary interventions (PCI) and have long posed a problem for interventional cardiologists.

Published data show bifurcation lesions treated using bare metal stents (BMS) have typical six to 18 month major adverse cardiovascular events (MACE) rates of 20–38% with one-stent strategies and 33–56% with two-stent strategies, and target lesion revascularisation (TLR) rates of 16–39% (see Table 1). Despite the advances in available equipment, bifurcation intervention is still associated with increased rates of complication when compared with non-bifurcated lesion intervention. There is a significantly lower probability of procedural success (86% versus 94%, p<0.001), with an increased rate of in-hospital MACE (7% versus 5%, p=0.1). At one year, treatment of bifurcation lesions is associated with significantly more MACE (32% versus 26%, p<0.05). A rise in cardiac enzymes, from loss or even temporary closure of a side branch (SB), has been shown to have a significant adverse effect on long-term outcome.

Therefore, the challenges of bifurcation PCI are preservation of both the main branch (MB) and SB, along with a reduction in restenosis and complication rates. The recent advances in interventional cardiology mean that now, for the majority of bifurcation lesions, the question is not whether to perform angioplasty, but to decide which type of stent to use, and which technique to use to maintain SB patency. In this article we will discuss what is known about bifurcation lesions at present, and what issues still need to be addressed.

The numerous different anatomical and angiographic variations of bifurcation lesions have given rise to a number of different classifications, which can be difficult to remember and compare when assessing results. Medina has recently proposed an easily memorizable classification, which makes description of the involved anatomy much simpler. He suggested using three components: MB proximal, MB distal and SB, with each component assigned a binary value (1,0) according to whether it is diseased or not (see Figure 1). The emergence of drug-eluting stents (DES) has led to re-evaluation of the treatment of bifurcation lesions given their proven reduced rates of TLR and restenosis in both simple and complex coronary disease. In bifurcation stenting DES have shown reduced rates of restenosis and MACE (see Table 1), but ostial SB restenosis remains a problem. Colombo et al. randomised patients to a one- or two-stent strategy using sirolimus-eluting stents (SES) and showed MB restenosis rates of 6%. The study confirmed that a two-stent strategy had a higher rate of SB restenosis (21% versus 14%); however, the results are of limited value because of a high cross-over rate (51%) from the one-to-two-stent strategy due to a sub-optimal result. Pan et al. also randomised patients with bifurcation lesions in a similarly designed study using SES, but had a crossover rate of only 2%. Their results also showed higher rates of restenosis in the MB (2% versus 10%) and SB (5% versus 15%) in the two-stent strategy, but this did not affect clinical outcome. The recently presented Nordic Bifurcation Study, which randomised 413 patients to a complex two-stent or single stent with provisional side branch stenting (PSBS) strategy using SES found no significant difference in the rate of MACE or TLR at six months.

In true bifurcation lesions, where significant plaque is present in both MB and SB, or lesions with thrombus, both branches should always be wired. Two guidewires offer several advantages, most notably maintaining a degree of antegrade flow and patency in the SB particularly if there is SB compromise after MB stenting. There is easier identification of the SB ostium, and also an advantageous change in the angle between the MB and SB, facilitating re-access. There are few associated risks with jailing the wire. Wire fracture is very rare and can minimised by avoiding large-diameter high-pressure deployment of the MB stent on a jailed wire. Patients with bifurcation lesions involving a small SB are best treated with a single stent to the MB with PSBS if required (see Figure 2). Even in the era of DES, restenosis is inversely related to stent diameter, and this is of particular importance in bifurcation lesions where the SB vessel diameter is often <2.5 mm; it would...
can be technically challenging and time consuming. Culotte stenting provides complete lesion coverage but is of adequate size (by FFR. In contemporary practice with DES, if the SB stenosed on angiography were functionally insignificant 27% of cases, while all lesions assessed to be <75% (Koo et al. found that angiographically significant lesions preventing unnecessary stenting of a compromised SB. Flow reserve (FFR) has been shown to be effective in SB is not reliably assessed by angiography, but fractional flow were left without additional treatment with no effect on clinical outcome. In addition, studies have shown that >60% of SB that are occluded immediately after SES stenting have spontaneously recanalised at follow-up. The need for intervention on a compromised SB is not reliably assessed by angiography, but fractional flow reserve (FFR) has been shown to be effective in preventing unnecessary stenting of a compromised SB. Koo et al. found that angiographically significant lesions (≥75% stenosed) were only functionally significant in 27% of cases, while all lesions assessed to be <75% stenosed on angiography were functionally insignificant by FFR. In contemporary practice with DES, if the SB is of adequate size (≥2.5mm), and the SB diameter stenosis is >50%, a strategy of two stents should be considered (see Figure 2). A variety of techniques exist to perform the two-stent strategy but the most effective stenting technique remains undefined. T stenting is best reserved for the 25% of lesions where the angle between branches is greater than 70 degrees. When this is not the case, T stenting risks incomplete coverage of the branch ostium – but this still remains a site for focal restenosis.

Single stent implantation with PSBS has been found to have the lowest rates of MACE and TLR when compared with more complicated techniques. A recent BMS multicentre study of 186 patients having single stenting with PSBS, in which 34% of patients had SB stenting, showed a seven-month TLR rate of 16% and MACE 23%. Event-free survival was significantly better with this technique when compared with a two-stent strategy of T stenting (75% versus 44%, p<0.05). Similar results have been obtained with the use of DES.

At present it is not known when intervention is necessary on an SB compromised by MB stenting. What is known is that the prognosis is favourable. In the study by Pan et al. with a very low rate of cross-over from a one- to a two-stent strategy, SB dissections with thrombolysis in myocardial infarction (TIMI) grade 3 flow were left without additional treatment with no effect on clinical outcome. In addition, studies have shown that >60% of SB that are occluded immediately after SES stenting have spontaneously recanalised at follow-up. The need for intervention on a compromised SB is not reliably assessed by angiography, but fractional flow reserve (FFR) has been shown to be effective in preventing unnecessary stenting of a compromised SB. Koo et al. found that angiographically significant lesions (≥75% stenosed) were only functionally significant in 27% of cases, while all lesions assessed to be <75% stenosed on angiography were functionally insignificant by FFR. In contemporary practice with DES, if the SB is of adequate size (≥2.5mm), and the SB diameter stenosis is >50%, a strategy of two stents should be considered (see Figure 2). A variety of techniques exist to perform the two-stent strategy but the most effective stenting technique remains undefined. T stenting is best reserved for the 25% of lesions where the angle between branches is greater than 70 degrees. When this is not the case, T stenting risks incomplete coverage of the branch ostium – but this still remains a site for focal restenosis.

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Pre-dilatation during bifurcation lesion intervention facilitates optimal stent deployment, and reduces the potential for ischaemia so that more time is available to accurately position stents. In addition this also gives information as to how the lesion will behave, such that if plaque shift occurs the strategy can be changed from one of PSBS to a two-stent strategy. The disadvantage is geographical miss, which must be avoided as it is a risk factor for restenosis. After the MB stent has been deployed, high pressure dilatation will facilitate re-wiring of the SB. Subsequent balloon inflation of the SB ostium, through the MB stent, will result in angiographically invisible stent deformation which occurs in the MB stent opposite the ostium of the SB. Kissing balloon post-dilatation is recommended to counteract this, and not only optimises the angiographic results but has also been shown to reduce in-hospital MACE, stent thrombosis and TLR. In crush stenting, failure to perform kissing balloon post-dilatation is an independent predictor of TLR (hazard ratio (HR): 4.17; 95% confidence interval (CI): 1.3–14.3; p=0.02), and associated with higher SB restenosis rates compared with those having final kissing balloon post-dilatation (11% versus 38%, p<0.001). In essence, two-stent strategies should always be optimised by kissing balloon post-dilatation.
Table 1: Summary of Trials Evaluating Percutaneous Coronary Intervention with Stent Implantation for Bifurcation Lesions

| Study                  | Length of FU (months) | Strategy                        | Number | In-hospital MACE (%) | Restenosis (%) | TLR (%) | MACE (%) |
|------------------------|-----------------------|--------------------------------|--------|----------------------|----------------|---------|----------|
| Bare metal stents      |                       |                                |        |                      |                |         |          |
| Pain et al             | 12                    | 1 stent                        | 4      | 4                    | 17             | 17      | 25       |
| Yokohama et al         | 6                     | 2 stents                       | 15     | 0                    | 26             | 26      | 76       |
| All Swendi et al       | 12                    | 1 stent                        | 77     | 3                    | 27             | 27      | 77       |
| Akasaka et al          | 12                    | 2 stents                       | 55     | 9                    | 59             | 59      | 77       |
| Ishibashi et al        | 7                     | 2 stents                       | 35     | 5                    | 63             | 63      | 76       |
| Drug-eluting stents    |                       |                                |        |                      |                |         |          |
| Colombo et al          | 6                     | 1 stent                        | 22     | 9                    | 19             | 19      | 25       |
| Fu et al               | 11                   | 2 stent                        | 47     | 4                    | 25             | 25      | 79       |
| Pan et al              | 11                   | 2 stent                        | 47     | 4                    | 25             | 25      | 79       |
| Sharp et al            | 6                     | 2 stents                       | 53     | 13                   | 53             | 53      | 76       |
| Tanabe et al           | 11                   | 1 stent                        | 208    |                      | 6              | 6       | 7        |
| Anzaniu et al          | 12                   | 2 stents                       | 54     | 0                    | 19             | 19      | 48       |
| Al Suwaidi et al       | 6                     | 2 stents                       | 53     | 13                   | 8              | 8       | 17       |
| Bifurcation stents     | Frontier stent        | 6                              | 102    | 3                    | 15             | 15      | 77       |
| Axxess Plus            | 6                     | Bifurcation stent              | 136    | 5                    | 8              | 8       | 77       |

FU = follow-up, MACE = major adverse cardiac event, TLR = target lesion revascularisation, MB = main branch, SB = side branch.

Studies have demonstrated relatively high rates of stent thrombosis (ST) when using DES in bifurcation lesions; in fact their use in this setting is an independent risk factor for ST (HR: 6.42; 95% CI: 2.93–14.07; p<0.001). This may partly be due to multiple layers of DES delaying endothelialisation. Poor compliance is also a very strong independent predictor of ST (HR: 89.78; 95% CI: 29.9–269.6; p<0.001) and therefore two-stent bifurcation strategies with DES should not be undertaken in patients who can’t or won’t comply with dual anti-platelet therapy. ‘Real-life’ studies suggest ‘acceptable’ ST rates of up to 1.6%; however, the risk appears to be higher in patients treated with a two-stent strategy. Ge et al. showed a rate of 3.9% in patients treated with two stents versus 0% in the single-stent group, and the two-stent group of Colombo’s randomised study had a particularly high ST rate of 6%.

Patients with complex coronary disease (including bifurcation lesions) have been shown to derive additional benefit with the use of stenting and glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa) compared with placebo. In clinical studies of bifurcation lesions, GPIIb/IIIa use is usually at the discretion of the operator, and therefore may only be used in complicated or difficult procedures; creating difficulty interpreting their effectiveness. However, in complex procedures involving two stents GPIIb/IIIa, use is recommended in view of the relatively increased risk of ST. An alternative is the use of Bivalirudin, which has not been specifically evaluated for bifurcation lesions but has been shown, in elective PCI, to be not inferior with regards to suppression of acute ischaemic events, and confers less risk of bleeding when compared with the combination of heparin and GPIIb/IIIa.

Several different dedicated bifurcation stents have been designed in order to address the procedural and clinical short comings of conventional bifurcation PCI. Designs have included stents with large cells between struts, bevelled stents for optimal SB ostium coverage, bifurcated stents, and also stent delivery systems that allow permanent access to the SB or reliable stenting of the SB ostium within the main branch stent. One of their main limitations is poor delivery as they are relatively bulky. The Multilink Frontier stent (Guidant) was evaluated in the Frontier registry and demonstrated a greater than 90% success rate. In the six-month MACE and TLR rates were comparable with the best results obtained utilising conventional BMS (see Table 1). Disadvantages of the stent were its large profile and poor flexibility making it more difficult to deliver in tortuous and calcified arteries; in addition it also required a guide catheter of at least 7 French. The six-month restenosis rate was 45%, suggesting that a drug-eluting dedicated stent was needed.

More recently the Axxess Plus DES has been developed, which is a self expanding nitinol stent that elutes Biolimus A9, a sirolimus analogue. The Axxess Plus trial was a multicentre single-arm registry of 136 patients that assessed the Axxess stent, implanted together with additional DES as necessary. Results were promising with MB and SB restenosis rates of 6% and 8% respectively. The late loss within the Axxess Plus stent was just 0.11 ± 0.62mm. At six months, the TLR rate was 8% and MACE 11%.

A version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchcardiology.com).