

## One or two stents for coronary bifurcation lesions?

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### Introduction

The question of the correct approach to bifurcation treatment has been a vexed one for over 20 years.<sup>1</sup> However, over the last five years, a number of randomised trials have taken place which has refined our understanding of the role of single versus dual vessel stenting for bifurcation lesions.

### Bare metal stents

There were no randomised trials specifically comparing simpler versus more complex strategies for treating bifurcation coronary artery disease with standard stents. Several important non-randomised comparisons were published.

– Al Suwaidi et al compared outcomes in 131 patients who underwent either stent placement in the main vessel and balloon angioplasty of the side-branch (n=77) or stent placement in both branches (n=54).<sup>2</sup> After one year of follow-up, no differences were seen in the frequency of major adverse cardiac effects (death, myocardial infarction or repeat revascularisation) between the groups.

– Yamashita et al examined 92 patients with bifurcation lesions treated either by stenting of the parent vessel with balloon angioplasty of the side-branch (n=39) or stenting of both vessels (n=53).<sup>3</sup> Target lesion revascularisation rates at six months were similar in the two groups at 36% and 38%, respectively.

– Anzuini et al undertook a further study in which 45 patients were treated with parent vessel stenting and balloon angioplasty of the

side-branch, while a further 45 were treated with stenting of both branches.<sup>4</sup> In this study, results favoured the simpler strategy, with target vessel revascularisation in 15% of patients from the simpler group compared with 35% of the complex group at one year.

These studies did not suggest a benefit, when using bare metal stents, in stenting both vessels rather than one, and in the bare metal era the provisional T stent approach was accepted as the gold standard methodology.

### Drug-eluting stents

Drug-eluting stents have been shown to have an extremely low incidence of in-stent restenosis (0%) compared with bare metal stents (26%) when used to treat single vessel lesions.<sup>5</sup> With the advent of these stents, the question of the appropriateness of a more complex approach to bifurcation lesion treatment was again assessed, this time in a number of randomised studies.

– Colombo et al compared a strategy of stenting the main vessel alone versus stenting both vessels using the modified T-stent technique in a study of 85 patients.<sup>6</sup> The modified T-stent technique was in fact employed in the majority of patients, as there was a very high crossover rate from single to dual vessel stenting. Analysis by intention-to-treat was therefore not meaningful. Angiographic restenosis (>50% in either vessel) was seen in 28% of the stent-stent versus 18% of the provisional stent group.

– Pan et al compared a simple strategy of main vessel stenting and side vessel dilatation (without kissing inflation) versus a systematic

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T-stent strategy in 91 patients.<sup>7</sup> There were no statistical differences in clinical or angiographic parameters between the two groups either acutely or after six months follow-up. Ostial side branch restenosis was observed in the two-stent strategy and this was thought to be due to incomplete lesion coverage inherent to the T-stent technique.

– Steigen et al undertook a randomised comparison of main vessel stenting versus stenting of both the main vessel and side branch using several different techniques (the NORDIC study).<sup>8</sup> In this large trial which used sirolimus-eluting stents, a very low rate of major adverse cardiovascular events was seen in both groups at six month follow-up (2.9% vs. 3.4%, respectively). Periprocedural biomarkers were more frequently elevated to myocardial infarction threshold in the dual stenting group but were only obtained in 68% of cases. Angiographic follow-up at eight months showed  $\geq 50\%$  lesion in the main vessel plus occlusion of the side branch in 5% of cases in both groups.

– In the BBC ONE study, Hildick-Smith et al randomised patients with bifurcation lesions (82% true lesions) to either a minimalist provisional T-stent strategy or full lesion coverage with either culotte or crush according to operator preference.<sup>9</sup> A significant difference was observed between the MACE rate in the complex group (15%) vs. that in the simple group (8%). This was largely driven by a higher incidence of periprocedural myocardial infarction (CK  $>3$  times) in the complex group.

– In the CACTUS study,<sup>10</sup> 350 patients with coronary bifurcations were randomised to crush or provisional T-stenting using sirolimus stents. Kissing balloon inflations were mandated in both groups, and were achieved in 92% and 90%, respectively. The primary clinical endpoint (6-month MACE) was similar in the two groups (16% vs. 15%), and there was no difference in the rate of angiographic restenosis in either the main or side branch.

– Ferenc et al compared the systematic T and the provisional T strategies in a later study of 202 patients and found no difference in target lesion revascularisation or ostial side branch restenosis at one-year follow-up.<sup>11</sup>

The general consensus from these studies was that there was no systematic advantage to a two-stent strategy for bifurcation lesions, even for true bifurcation lesions. The main disadvantage to this strategy was seen in terms of periprocedural myocardial infarction. The significance of periprocedural myocardial infarction has been argued in both directions, and at present there seems consensus that CK release  $>8$  times ULN or CK-MB  $>5$  times ULN is certainly of significance, but that lesser levels may not be of importance.<sup>12,13</sup>

## Meta-analyses

After the publication of these trials, multiple meta-analyses were published without patient level data. Such analyses can be misleading.<sup>14</sup> A patient-level meta-analysis of the BBC ONE and NORDIC trials has since been made.<sup>15</sup> This analysis of 913 patients confirmed the findings of the individual studies and furthermore demonstrated no significant superiority for a two-stent strategy among more complex patient groups, such as those with large side branches and those with  $>5$  mm length ostial side branch disease.

## Limitations of a two-stent strategy

Two-stent strategies remain popular with a minority of operators who are very familiar with the techniques. There are however limitations to the two-stent strategy, in terms of consumables, technique and outcomes:

### Consumables

All studies comparing single and dual-stent techniques have shown increased fluoroscopy time, X-ray dose and contrast use with the complex strategy. In addition, coronary guidewire, balloon and stent use are all significantly greater in the more involved procedure.<sup>9</sup>

### Technique

Two-stent techniques are more exacting in terms of wire exchanges, recrossing of stent struts, stent delivery and kissing balloon inflations. They are also less forgiving with respect to coronary calcification, tortuosity and vessel angulation. Final kissing balloon inflations are important for optimal technical results. However, in the combined NORDIC and BBC ONE trials, final kissing balloon inflation was only achieved in 75% of systematic two-stent cases.<sup>15</sup>

### Outcome

An optimally-undertaken two-stent technique is likely to have as good an outcome as a provisional T-stent strategy. However, the complexity of the two-stent procedure limits the proportion of cases in which the procedure can be said to have been completed optimally. And while there is no difference between the techniques in terms of death and target vessel revascularisation, the increased periprocedural myocardial infarction seen with two-stent techniques is unlikely to be advantageous. Stent thrombosis is now thankfully relatively rare. In the randomised studies, no increase in stent thrombosis rates has been seen for the two-stent approaches, but in the J-Cypher Registry, two-stent techniques were associated with an odds ratio of 1.8 (1.2-2.6) for late or very late stent thrombosis.<sup>16</sup> Finally, an important observation of the meta-analysis of NORDIC and BBC ONE showed that if patients require repeat revascularisation of a bifurcation lesion, an initial two-stent strategy renders them highly likely to be referred for coronary artery bypass grafting, whereas an initial one-stent strategy usually allows repeat percutaneous coronary intervention.<sup>15</sup>

## Two-stent techniques

A plethora of techniques exist, supported by limited prospective data. The only randomised study on the subject allocated patients to either crush or culotte stenting. At six months clinical follow-up, there was no difference between the two groups in terms of death, postprocedure MI or revascularisation (crush 4.3% vs. culotte 3.7%). However, the incidence of periprocedural MI was significantly higher in the crush group (crush 15.5% vs. culotte 8.8%) as was the occurrence of in-stent restenosis (crush 10.5% vs. culotte 4.5%).<sup>17</sup> In accordance with other studies, the ability to complete the crush technique with final kissing balloons was lower than for the culotte technique. The double-kiss crush technique has been evolved to counter this drawback,<sup>18</sup> but adds further

complexity to an already demanding procedure. Final kissing balloon inflations are very important for success in two-stent approaches, and ideally should be undertaken with non-compliant balloons. High pressure individual “ostial” and final proximal stent inflations are also required to correct stent deformation.

### European Bifurcation Club consensus

The consensus from the most recent meeting of the European Bifurcation Club<sup>19</sup> with regard to two-stent strategies was:

- Provisional T-stenting remains the gold standard technique for most bifurcations
- Large side branches with ostial disease extending >5 mm from the carina are likely to require a two-stent strategy
- Side branches whose access is particularly challenging should be secured by stenting once accessed. Kissing balloon inflation for carina reconstruction is mandatory in two-stent techniques
- Non-compliant balloons are recommended for kissing inflations
- Individual non-compliant high pressure “ostial” post-inflations are mandatory in complex stenting techniques to achieve full stent expansion
- High pressure proximal stent inflation using a short noncompliant balloon should be considered for correction of possible proximal stent distortion after kissing balloon inflation.

### Upcoming studies

Despite the adverse aura surrounding the two-stent techniques, experienced bifurcation operators still believe that there is a subgroup of patients in whom double stenting may be specifically of value. These patients are thought to be those with large side branches (>2.5 mm diameter) in whom the side branch has ostial disease for more than 5 mm length. In these patients, the side branch appears to merit stenting in its own right on anatomical and physiological grounds. They are therefore the subject of the upcoming NORDIC IV and EBC TWO studies, which will randomise patients to either a systematic dual stent strategy or a main vessel stent with mandatory kissing inflations.

It seems highly likely that these two studies to be the last taking true bifurcations (non-left-main) and randomising them to a two-stent versus a one-stent strategy. In fact, some experienced operators in the field believe the “one-stent-versus-two” question to be obsolete, arguing that there is limited downside to undertaking a two-stent strategy if that is a) what is required, or b) what the operator is most experienced with. The authors of this paper would not necessarily demur from this viewpoint.

### Left main stem bifurcation stenting

When operators starting undertaking left main stem bifurcation stenting, many investigators expected this to be an area where the two-stent strategy might prove superior, largely because the “side branch” is in fact a major epicardial vessel in its own right and should not be ignored. However, thus far, the opposite has proven to be the case. All published series have shown better outcomes with single vessel stenting rather than dual,<sup>20-23</sup> though no randomised studies yet exist. The main reason for this worse outcome may lie in the angles of the left main bifurcation, which are

more divergent than in other parts of the coronary tree.<sup>24</sup> This anatomical feature therefore militates against a good result considering the difficulty of conforming stents to acute curves while maintaining good wall apposition throughout. Certainly this would be in keeping with data from non left main bifurcations, in which worse outcomes are seen with greater degrees of angulation of the bifurcation.<sup>25,26</sup>

### Dedicated bifurcation systems

Dedicated bifurcation stent systems have had a hard time over the last few years. The excellent clinical outcomes seen particularly in the NORDIC trial have dampened enthusiasm for more complex technologies, at least in the short term. Nonetheless it is a truism to say that neither culotte stenting nor provisional T are likely to be the final answer in bifurcation stenting. At the recent European Bifurcation Club meeting, a “show of hands” demonstrated that more than 50% of the attendees believed that within five years we will have dedicated bifurcation stent systems in routine clinical use. This may be particularly true for the left main stem, where bulkier devices may be delivered with greater ease.<sup>27</sup> Numerous ingenious dedicated systems are in development, and we can expect these to play a major role in the coming years.

### Conclusions

The majority of coronary bifurcation lesions should be treated using a single-stent strategy. More important than the issue of whether a one-stent or a two-stent strategy should be used is to ensure that the procedure is done to a high standard, with a good understanding of the role of adjunctive techniques such as proximal optimisation and kissing balloon inflations.

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