Safety Issues Related to Treating Bifurcation Lesions

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Treating bifurcation lesions is a challenge in interventional cardiology. There is evidence that the anatomic morphology of the lesions plays a role not only in procedural success and complication rates, but also in the selection of stenting technique. Bifurcation angle, assessment of lesion severity, and acute stent thrombosis all pose a challenge to the interventionist. Safety issues related to treatment of bifurcation coronary disease is discussed. Assessment of lesions both before and after stenting using intravascular ultrasound in addition to quantitative coronary angiography may result in fewer complications.

[Rev Cardiovasc Med. *2010;11(suppl 1):S3-S10 doi: 10.3909/ricm11S1S0002*]

Key words: Angulation • Bifurcation lesions • Classification systems • Stenting strategies

Numerous technical challenges face the operator planning to intervene therapeutically on a coronary bifurcation lesion using straight, concentric tubular catheter systems. Despite the lack of a universal definition, a bifurcation lesion can generally be defined as a lesion occurring near the branch point of 2 epicardial coronary vessels that are likely to be hemodynamically significant. The detailed pathologic description of a complex atherosclerotic lesion at the bifurcation of a left main coronary artery was first described in 1983.[1] Since that time it has been understood that these lesions can be irregular, generally related to the vessel curvature and flow dynamics that result from the vessel geometry. Furthermore, the early National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry and American College of Cardiology/American Heart Association Task Force analysis reported that anatomic features of coronary lesions, including bifurcation lesions, play a role in procedural success and complications.[2,3]

Several classification systems have been developed to characterize the various bifurcation lesions. Many of these systems are problematic due to their redundancy or the difficulty in applying them to relevant clinical scenarios. The Medina classification system[4] attempts to simplify lesion characterization by simply dividing bifurcation lesions into 3 segments, with each assigned a number: a proximal segment of the main branch (MB), side branch (SB) ostium, and distal segment of the MB. If the segment within the lesion has > 50% stenosis it will receive the suffix 1, otherwise suffix 0 is assigned, respectively. For example, lesion 0,1,1 means that the proximal segment is uninvolved, but the SB ostia and MB at or beyond the vessel carina both have disease. This classification system has been endorsed by some interventional groups but has been criticized by others for its failure to include the angulation of branches and the size of the proximal segment. Clearly, not all bifurcation lesions are created equal within this (or any other) classification system (Figure 1).

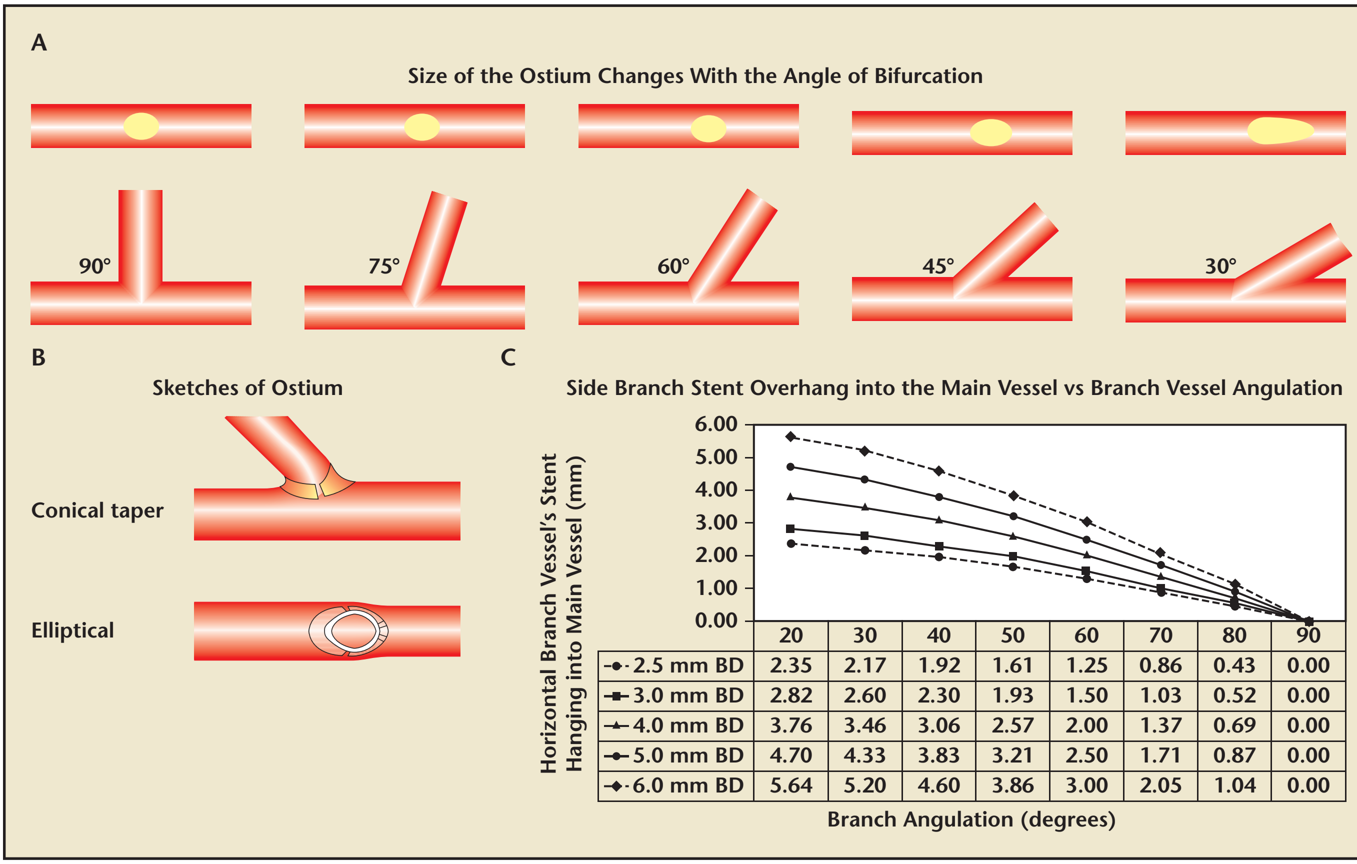
A number of complex technical factors play a role in interventions on coronary bifurcation. For the purpose of simplicity, these factors can be grouped into 3 broad categories: SB access challenges, vessel injury, and scaffolding-related issues. SB access can complicate or distort the stent architecture or result in inability to access the distal MB. Vessel "injury" can result from stent protrusion into one of the bifurcation branches; there is an increased risk of dissection when treating bifurcation lesions, and the rates of restenosis are increased with percutaneous interventions compared with nonbifurcation lesions. Finally, there may be anatomic scaffolding issues with stents in bifurcating lesions such as gaps between stents, incomplete apposition, or multiple strut layers.

Bifurcation Angulation

These factors contribute to Murray's law, a theoretical explanation for the relationship between the radius of an artery upstream from a branch point and the radius in the downstream vessel.

Just beyond the ostium of the SB there is likely to be tapering of the vessel (Figure 2B). These factors will contribute to the smaller luminal area following an intervention and contribute to restenosis of the SB. In addition, the more acute the angle of the SB take-off from the MB the greater the risk of horizontal stent overhang into the main vessel (MV),[5] which can contribute to layers of metal in the MV after a second stent is deployed in the MB (Figure 2C). As the metal to artery lumen ratio increases there is an increased risk for restenosis.[6] This ratio has previously been described as the metal/artery index, defined as $\alpha P/\alpha V$, where αV is the angle described by the slot and αP is the angle described by the metal in the cross-section of the

Figure 1. *Bifurcation classification by the Medina system showing various characterizations of coronary lesions.*



	20	30	40	50	60	70	80	90
2.5 mm BD	2.35	2.17	1.92	1.61	1.25	0.86	0.43	0.00
3.0 mm BD	2.82	2.60	2.30	1.93	1.50	1.03	0.52	0.00
4.0 mm BD	3.76	3.46	3.06	2.57	2.00	1.37	0.69	0.00
5.0 mm BD	4.70	4.33	3.83	3.21	2.50	1.71	0.87	0.00
6.0 mm BD	5.64	5.20	4.60	3.86	3.00	2.05	1.04	0.00

Figure 2. **(A)** *As the angle of bifurcation changes, the side branch (SB) ostial dimensions changes from a more cylindrical shape at 90° to a more elliptical shape as the angle approaches zero.* **(B)** *Graphic depiction of the tapering effect that occurs in the SB after a bifurcation.* **(C)** *Graph showing the relationship between the main vessel diameter, angle of the bifurcation, and the horizontal branch vessel stent overhang distance. With kind permission from Springer Science + Business Media:* Cardiovascular Engineering: An International Journal, *"Theoretical analysis of bifurcating branch vessel geometry for stents," Vol. 5, 2005, pp. 127–134, K. Khaw and H. Crow, Figure 4, © 2005 Springer Science + Business Media, Inc.*[5]

unexpanded configuration.[7] Interestingly, bifurcation angles have been shown to vary depending on the parent coronary vessel. The steepest angle (defined as < 110°) is generally found in the left main bifurcation (26%), followed by left circumflex (LCX) (15%), and right coronary distal bifurcation (12%). This was reported in a study using 64-slice multidetector computed tomography to assess coronary vessel geometry in 209 patients presenting with chest pain.[8] The average left anterior descending (LAD) and LCX angle was 72°.

Bifurcation angle not only contributes to procedural difficulties and higher rates of restenosis but has also been associated with increased mortality and major adverse cardiac events (MACE). Dzavik and colleagues[9] reported their findings in 133 patients undergoing bifurcation interventions with a crush technique and found that high angle (defined as > 50°; n = 67) was associated with higher MACE rates as compared with the low-angle group (defined as < 50°; n = 66) (22.7% vs 6.2%; P = .007). Although the differences in individual MACE events did not reach statistical significance each of the events occurred more frequently in the high-angle group compared with the low-angle group (myocardial infarction [MI] 4.8% vs 0%, target lesion revascularization [TLR] 12.3% vs 3.1%, coronary artery bypass graft 4.7% vs 1.5%, and death 6% vs 1.5%). These findings were confirmed from analyses of the French

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Left Main Taxus registry. For the purpose of this analysis the bifurcation angle was classified as a T-shape or a Y-shape depending on the take-off angle of the SB—Y-shape when the bifurcation angle was < 70° and T-shape when the angle was > 70°. This classification was used initially by Vaquerizo and colleagues[10] to define better treatment strategies in bifurcation lesions. T-shape, or higher, bifurcation angles were associated with higher risk of stent thrombosis, cardiac death, and death at 2-year follow-up (Table 1).[10]

Assessment of SB Lesions Before and After Intervention

Assessing SB lesion severity also poses challenges. A recent report by Koo and coworkers[11] compared the assessment of SB lesion severity with quantitative coronary angiography (QCA) and fractional flow reserve (FFR). The study enrolled 97 consecutive patients with jailed SB lesions, defined as a vessel size > 2.0 mm and stenosis > 50% by visual estimation, and performed successful FFR on 94 of these patients. They found a negative correlation between the percentage of stenosis and FFR ($r = -0.41$; $P < .001$), but no lesion with < 75% stenosis by visual assessment had FFR < 0.75, and only 20 of the 73 lesions with ≥ 75% stenosis were functionally significant (Figure 3). Therefore, this study indicated that most stenotic SBs do not have functional significance as assessed by FFR.

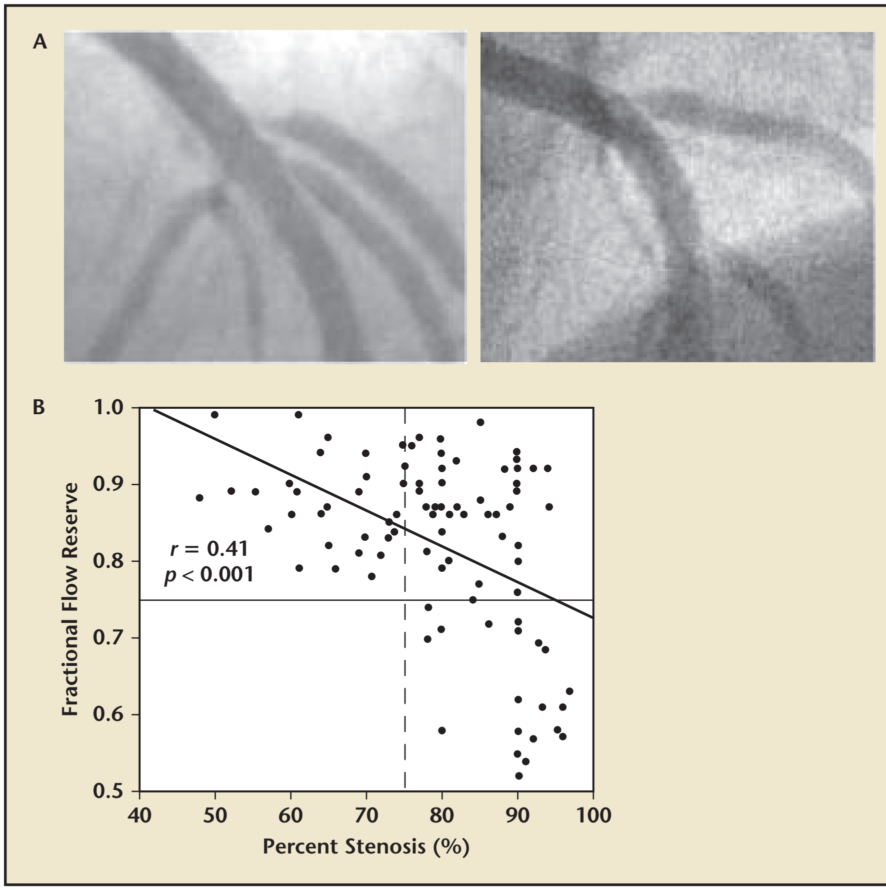

Figure 3. **(A)** *Diagnostic considerations in ostial side branch (SB) lesion severity after SB jailing.* **(B)** *Physiologic assessment of a jailed SB lesion using fractional flow reserve and correlation between fractional flow reserve and percent of stenosis. The optimal cutoff value for percent stenosis to predict functionally significant stenosis was 85% (sensitivity: 0.80, specificity: 0.76). Figure 3B reprinted from* Journal of the American College of Cardiology, *Vol. 46, BK Koo et al, "Physiologic assessment of jailed side branch lesions using fractional flow reserve," pp. 633-637, Copyright 2005, with permission from the American College of Cardiology Foundation.*[11]

In addition, using angiography to assess results following a SB intervention with a stent may have limitations. In a study by Costa and coauthors,[12] 40 patients with bifurcation lesions underwent crush-stenting with the sirolimus-eluting stent. Postintervention intravascular ultrasound (IVUS) was performed in both branches in 25 lesions and only the MV in 15 lesions. Not surprisingly, it showed the minimal stent area to be smaller in the SB than the MV (6.5 ± 1.7 mm^2 vs 3.9 ± 1.0 mm^2; $P < .0001$). However, the majority of SB lesions showed stent under-expansion (60%) and stent under-expansion detected

Table 1
French Left Main Taxus Registry: Role of Bifurcation Angle

2-Year Follow-Up	Y-Shape	T-Shape	*P* Value
Stent thrombosis (%)	0	2.3	< .05
TVR (%)	8.7	8.3	.41
Cardiac death (%)	2.9	9.5	.021
Death (%)	4.4	17.8	.001

TVR, target vessel revascularization.
Percentages expressed as means.

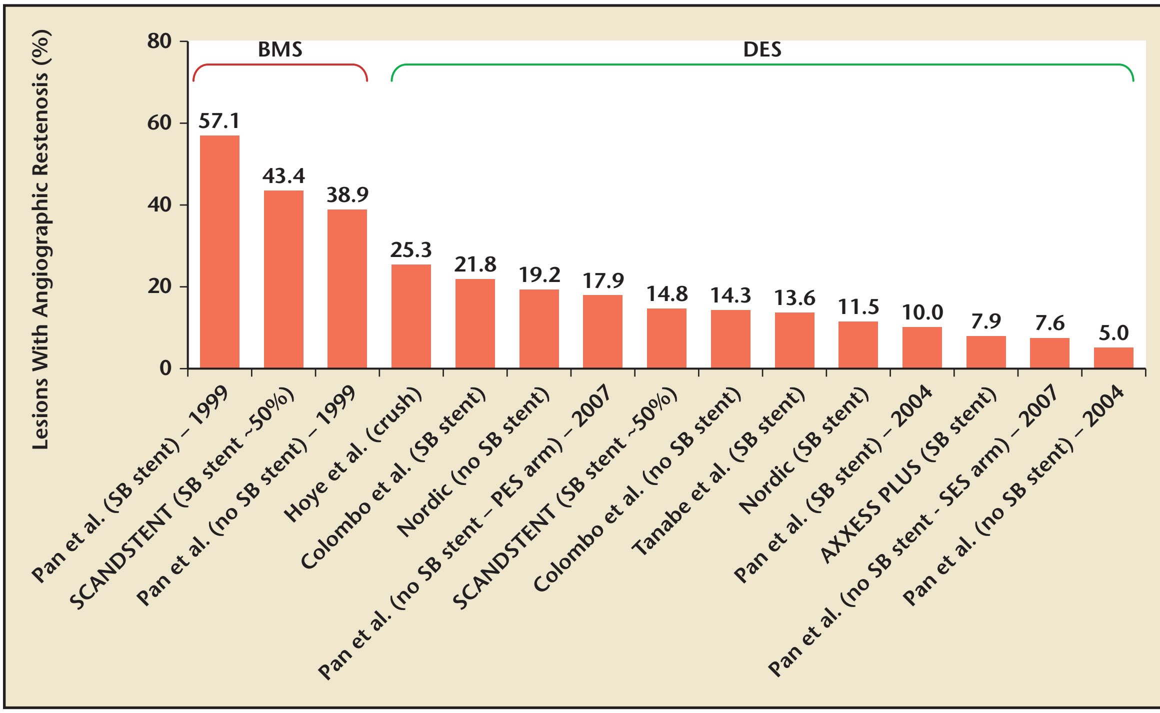

Figure 4. *Evolution of side branch restenosis in bifurcation series. BMS, bare metal stent; DES, drug-eluting stent. SCANDSTENT, Stenting Coronary Arteries in Non-stress/Benestent Disease.*

by IVUS that were not suspected angiographically. Incomplete crushing, defined as incomplete apposition of SB or MV stent struts against the MV wall proximal to the carina, was most commonly associated with SB stent underexpansion (77.1 ± 7.6% vs 89.4 ± 13.1%; P = .04).

Bifurcation Lesions and Acute Stent Thrombosis

Bifurcation lesions have been reported as an independent predictor for increased rates of stent thrombosis. The low frequency of stent thrombosis makes the subset analysis of bifurcation lesions challenging. However, a multivariate analysis of a high-risk group of patients with stent thrombosis found that renal failure (odds ratio [OR] = 11.5), bifurcation lesions (OR = 7.2), prior brachytherapy (OR = 4.2), diabetes (OR = 3.4), and a low left ventricular ejection fraction (OR = 1.1) increased the risk of stent thrombosis.[13] This has led to the empirical recommendation that antiplatelet therapy be intensified following bifurcation interventions.

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Simple Versus Complex Stenting

Perhaps one of the first considerations when planning a percutaneous intervention on a bifurcation lesion is whether to use a single stent (simple strategy) or multiple stents. A 2-stent strategy, generally involving at least 1 stent in the MV and 1 stent in the SB, is fraught with challenges and is generally referred to as a “complex” strategy. The drug-eluting stent (DES) era has generally improved rates of restenosis following bifurcation interventions (Figure 4), but several challenges remain. A 2-stent procedure makes wire management more difficult; stent proximity techniques (eg, kissing, crush) must be decided on, with stent overlap generally leading to delayed endothelialization and increased rates of restenosis, even with DES. Using 2 stents increases the risk of poor stent apposition due to under-expansion, and also increases the chances of stent fracture.

The impact of a 2-stent strategy was reported from the distal left main registry of the GISE-SICI (Gruppo Italiano Studi Emodinamici-Società

Table 2
Impact of Bifurcation Technique in Distal LMCA PCI: GISE-SICI

2-Year Follow-Up	1 Stent (n = 456)	2 Stents (n = 317)	*P* Value
Survival (%)	90.4	92.2	.77
MACE-free survival (%)	75.3	67.6	.02
TLR-free survival (%)	87.0	73.1	< .001

GISE-SICI, Gruppo Italiano Studi Emodinamici-Società Italiana di Cardiologia Invasiva; LMCA, left main coronary artery; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; TLR, target vessel revascularization.
Percentages expressed as means.
A single-stent strategy was an independent predictor of lower MACE.
As an extreme case, 2 other studies demonstrate MACE rates > 30% with trifurcation disease.

Italiana di Cardiologia Invasiva) study.[14] In this retrospective observational study of 773 patients with 2-year follow-up, the risk-adjusted survival free from MACE was significantly higher in patients receiving 1 stent compared with those receiving 2 stents. Comparing patients who received 2 stents (n = 317) with those who received 1 stent (n = 456) the adjusted hazard ratio (HR) for risk of 2-year MACE was 0.53 (95% confidence interval [CI], 0.37-0.76), and the propensity-adjusted HR for the risk of 2-year cardiac mortality and MI in patients in group 1 versus group 2 was 0.38 (95% CI, 0.17-0.85) (Table 2).

A smaller prospective single center study conducted between March 1993 and April 1999 with a total of 92 patients undergoing coronary stenting for symptomatic bifurcation lesions showed different results.[15] This study compared 2 strategies for treating bifurcation lesions: use of a single stent in only the parent vessel of the bifurcation lesions and balloon angioplasty of the SB (n = 39 patients) versus stenting of both branches of the bifurcation lesion (n = 53 patients). In-hospital MACE (predominantly cardiac enzyme elevation) occurred only in the 2-stent group (13% vs 0%; *P* = .05), and at 6-month follow-up the angiographic restenosis rate (62% vs 48%), TLR (38% vs 36%), and MACE (51% vs 38%) were higher in the 2-stent group, although none met statistical significance. Several factors complicate the results of this study—first, there was more debulking prior to stenting in the 2-stent group. Also, many different stenting techniques were used in the 2-stent group (T-stent [30%]; Y-stent [26%]; V-stent [28%]; culotte [15%]) making conclusions about any particular technique difficult.

Two recent meta-analyses comparing simple (single stent) versus complex (2 or more stents) treatment strategies for bifurcation lesions have been published. The first included 5 studies with a total of 1145 patients and compared the clinical and angiographic outcomes of a double-stent technique (stenting of the MB and SB; n = 529) to the single-stent technique (stenting of MV only with balloon dilation of the SB; n = 616) for treatment of bifurcation lesions with DES.[16] As would be expected, postprocedural minimal lumen diameter of the SB was significantly smaller in the single-stent group. However, the odds of SB restenosis, MB restenosis, all-cause mortality, MI, and TLR were similar between the 2 groups. The authors therefore concluded that patients undergoing percutaneous coronary intervention (PCI) for true coronary bifurcations have no added advantage of stenting both branches as compared with a conventional single-stent strategy.

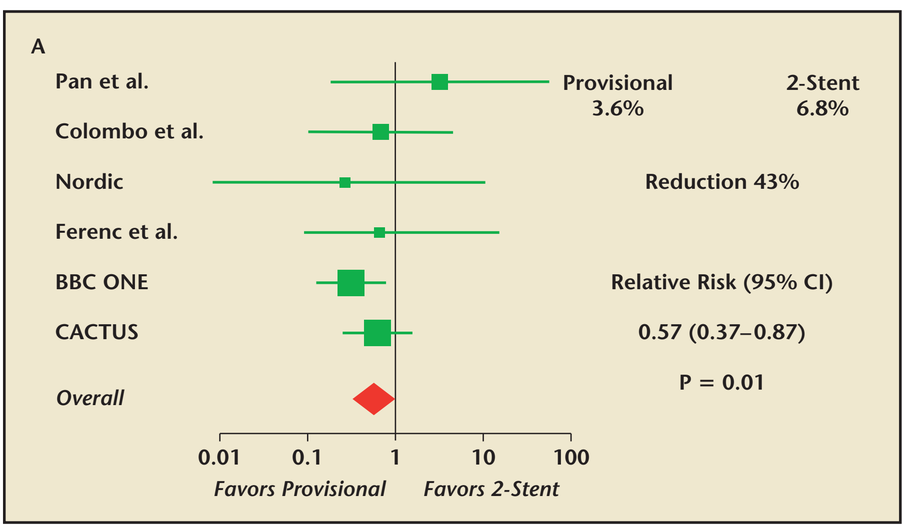
A second meta-analysis also included 5 trials, with a total of 1553 patients, and showed significantly lower rates of late MI (relative ratio [RR] 0.54; 95% CI, 0.37-0.78; *P* = .001), at 6 months, as well as early (in-hospital or 30-day) MI (RR 0.52; 95% CI, 0.35-0.78; *P* = .002) in patients treated with the simple strategy compared with the complex strategy.[17] There were no significant differences between the 2 strategies with respect to the rates of cardiac death (RR 0.68; 95% CI, 0.21-2.25; *P* = .53), TLR (RR 0.93; 95% CI, 0.62-1.41; *P* = .74), or stent thrombosis (RR 0.50; 95% CI, 0.19-1.32; *P* = .16). The restenosis risk of MV and SB did not differ between the simple-strategy group and the complex-strategy group (RR 1.15; 95% CI, 0.66-2.00; *P* = .63 and RR 1.12; 95% CI, 0.80-1.57; *P* = .50, respectively). Again, the authors concluded that a more complex strategy with DES treatment of coronary bifurcation lesions was associated with increased risk of early MI and similar rate of angiographic restenosis compared with a simple strategy. They went on to recommend the simple strategy as the preferred bifurcation stenting technique in the DES era.

As mentioned earlier, there are multiple techniques used in the complex approach to bifurcation lesions, and there is evidence to suggest that certain techniques may be preferable to others. A recent study with DES compared the crush technique to the simultaneous kissing stent (SKS) technique in bifurcation lesions in 74 consecutively enrolled patients with 3 years of follow-up.[18]

In-hospital outcomes were not significantly different between the 2 groups. Over a median follow-up of 3.3 years, 1 patient in the SKS group and 3 patients in the crush group died (*P* = not significant). Using definitions of stent thrombosis set forth by the Academic Research Consortium, probable stent thrombosis leading to death occurred in 1 patient in the crush group (no definite stent thromboses were noted). Mortality in the remaining 3 patients was noncardiac. TLR occurred in 14 patients (40%) in the SKS group and 5 patients (12.8%) in the crush group (*P* = .015). Survival free from MACE was significantly less in the SKS group and predominantly driven by TLR (60 vs 88%; *P* = .001). Thus the authors concluded that TLR and MACE were significantly lower in bifurcation lesions treated with the crush technique when compared with the SKS technique, and that definite or probable stent thrombosis is rare with either technique.

A recent review and meta-analysis compared a provisional (elective SB stenting) to a routine 2-stent strategy (mandatory SB stenting) for the treatment of bifurcation lesions.[19] Only the relative risk for MI within 1 year of the index procedure reached a statistical significance of 0.57 (0.37-0.87) (Figure 5A), whereas death, TLR, and stent thrombosis were not significantly different. In addition, by QCA there was no difference in means (95% CI) between the provisional and 2-stent strategies for the percentage of diameter stenosis in the MV or SB (Figure 5B).

Notwithstanding the results of these studies, one should recognize that they all included lesions that could be treated with either technique and therefore excluded lesions that the operators had selected for the 2-stent approach from the beginning. Features of such lesions are



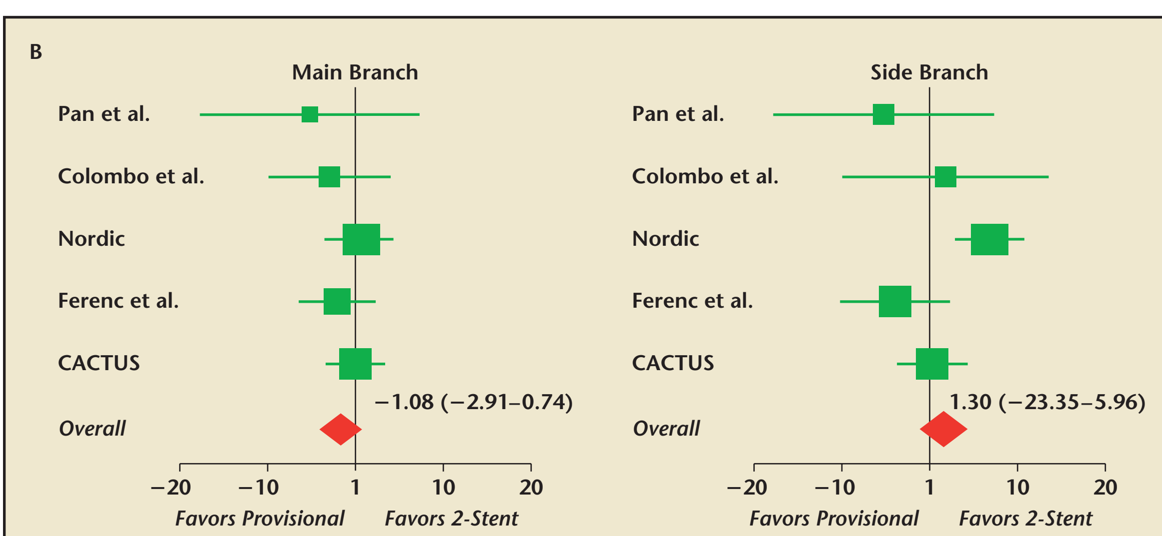


Figure 5. (A) *A bifurcation stenting meta-analysis demonstrating a relative risk of 0.57 (*P = *.01) favoring a provisional stenting strategy over a dedicated 2-stent approach.* **(B)** *Quantitative coronary angiography (QCA) analysis in the main branch (MB) and side branch (SB) comparing the percentage of diameter stenosis (difference in means) between a provisional strategy and a dedicated 2-stent strategy. BBC ONE, British Bifurcation Coronary Study; CACTUS, Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents.*

mostly related to the combination of high-level stenosis and angulation at the SB, a relatively large reference diameter, and an important downstream myocardial distribution supplied by the SB. Another parameter is the length of disease beyond the SB ostium that would indicate high likelihood of dissection after balloon dilation, especially if combined with calcification. In fact, a recent analysis from the Nordic trial, presented at the 2009 Transcatheter Cardiovascular Therapeutics conference, brought into question the utility of any intervention at all within a SB.

Conclusions

Treating bifurcation lesions remains a challenge in interventional cardiology and will be the focus of continued investigation moving forward. The Medina classification for characterizing bifurcation lesions is a simple-to-use system but is not without limitations. An effort to limit stenting in small SBs with focal disease using a provisional stenting technique would appear warranted. However, there will always be a minority of bifurcation lesions that will warrant treatment with 2 stents. The use of IVUS or FFR to assess SB lesions before and following an intervention may limit future complications. ■

Dr. Saltzman has no real or apparent conflicts of interest to report. Dr. Mehran and Dr. Dangas have received honoraria from Cordis Corporation, Medtronic, Inc., Abbott Vascular, and Boston Scientific Corporation.

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Main Points

- A number of complex technical factors play a role in interventions on coronary bifurcation. These factors can be grouped into 3 broad categories: side branch (SB) access challenges, vessel injury, and scaffolding-related issues.
- The angulation of a SB, as it shifts from an oblique angle to a more perpendicular angle, changes the size of the orifice at the SB ostium. A more perpendicular take-off and smaller orifice pose a series of challenges for wiring and intervening on a SB. Bifurcation angle not only contributes to procedural difficulties and higher rates of restenosis, but has also been associated with increased mortality and major adverse cardiac events.
- Assessing SB lesion severity poses challenges. Using intravascular ultrasound in addition to angiography to evaluate results following an intervention may limit future complications.
- Because bifurcation lesions are an independent predictor for increased rates of stent thrombosis, intensification of antiplatelet therapy following interventions is recommended.