**Circulation: Cardiovascular Interventions Topic Review**

**Most Important Articles on Bifurcation Disease**

The Editors

The following are highlights from the series, *Circulation: Cardiovascular Interventions* Topic Review. This series summarizes the most important articles, as selected by the editors, which have been published in the *Circulation* portfolio. The studies included in this article represent the most noteworthy research in the area of bifurcation disease. (*Circ Cardiovasc Interv*. 2012;5:e66-e69.)

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**Validation of Intravascular Ultrasound-Derived Parameters With Fractional Flow Reserve for Assessment of Coronary Stenosis Severity**

**Summary:** The authors assessed optimal intravascular ultrasound criteria for predicting functional significance of intermediate coronary lesions. Overall, 201 patients with 236 coronary lesions underwent intravascular ultrasound and invasive physiologic assessment pre-intervention. Fractional flow reserve (FFR) was measured at maximal hyperemia induced by intravenous adenosine infusion. FFR <0.80 at maximum hyperemia was seen in 49 (21%) of the overall 236 lesions. The independent determinants of FFR were minimal lumen area (MLA; β=0.020; 95% CI, 0.008–0.031; P=0.032), plaque burden (β=0.002; 95% CI, -0.003 to 0.001; P=0.001), lesion length with a lumen area <3.0mm² (β=-0.003, 95% CI, -0.005 to -0.001; P=0.005), and left anterior descending coronary artery location (β=-0.035; 95% CI, -0.055 to -0.016; P=0.001). The best cutoff value (with a maximal accuracy) of the MLA to predict FFR <0.80 was <2.4mm² with a diagnostic accuracy of 68% (90% sensitivity, 60% specificity, and area under the curve=0.800; 95% CI, 0.742–0.848; P<0.001). The cutoff value of plaque burden to predict FFR <0.80 was ≥7% (69% sensitivity, 72% specificity, and area under the curve=0.756; 95% CI, 0.696–0.810; P<0.001). Among 117 lesions with an MLA ≥2.4mm², 112 (96%) had an FFR ≥0.80, and all but 1 showed FFR ≥0.75. Conversely, 44 lesions (37%) with an MLA <2.4mm² had an FFR <0.80. Intravascular ultrasound-derived MLA ≥2.4mm² may be useful in excluding FFR <0.80, but poor specificity limits its value for physiologic assessment of lesions with MLA <2.4mm². Thus, FFR or some other functional assessment may be necessary to accurately identify ischemia-inducible intermediate stenoses.

**Conclusions:** Intravascular ultrasound-derived MLA ≥2.4mm² may be useful in excluding FFR <0.80, but poor specificity limits its value for physiological assessment of lesions with MLA <2.4mm². Thus, FFR or stress tests may be necessary to accurately identify ischemia-inducible intermediate stenoses.1

**Simple or Complex Stenting for Bifurcation Coronary Lesions: A Patient-Level Pooled Analysis of the Nordic Bifurcation Study and the British Bifurcation Coronary Study**

**Summary:** Controversy persists regarding the correct strategy for the treatment of coronary bifurcation lesions. The authors have carried out a pooled analysis of patient-level data of 913 patients enrolled in 2 randomized trials comparing a simple stenting strategy (stenting of main vessel and provisional treatment of side branch) with a complex strategy (stenting both main vessel and side branch) using drug-eluting stents. Clinical follow-up of these 2 groups up to 9 months showed a 10.1% major adverse event rate in the simple group versus a 17.3% major adverse event rate in the complex group. The difference was largely driven by peri-procedural myocardial infarction. Procedure duration, contrast volume, and x-ray dose exposure favored the simple group. In addition, a subgroup analysis of more anatomically complicated lesions demonstrated no benefit of a complex strategy. This study, therefore, suggests that the usual strategy for the treatment of bifurcation lesions should be the simple provisional strategy.

**Conclusions:** For bifurcation lesions, a provisional single-stent approach is superior to systematic dual-stenting techniques in terms of safety and efficacy. A complex approach does not seem to be beneficial in more anatomically complicated lesions.2

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**Intravascular Ultrasound Classification of Plaque Distribution in Left Main Coronary Artery Bifurcations: Where Is the Plaque Really Located?**

**Summary:** Using gray-scale intravascular ultrasound, the authors assessed 140 left main coronary artery (LMCA) bifurcations with moderate-to-severe disease, evaluating the longitudinal and circumferential distributions of atherosclerotic plaques with the main purpose to establish the first intravascular ultrasound classification of distal LMCA bifurcation lesions and to provide better insight into the pathology of the LMCA bifurcation. Extending the system proposed by Medina et al, the authors’ scheme illustrates 7 types of longitudinal plaque distribution, with detailed explanation regarding the spatial orientation toward the myocardium, pericardium, or lateral wall of the vessels. In general, this analysis shows more extensive axial plaque distribution from the LMCA into the ostial/proximal left anterior descending and left circumflex arteries than is apparent angiographically and consistent sparing of the carina. However, despite angiographic assessment and irrespective of standard angiographic and intravascular ultrasound morphologies, 90% of distal LMCA bifurcations fit 1 of 3 patterns: LMCA disease extending into the left anterior descending and left circumflex arteries; LMCA disease extending into the left anterior descending but not the left circumflex artery; and LMCA disease extending into the left anterior descending artery with focal disease at the ostium of the left circumflex artery. The authors hope that this proposed scheme may help to establish that preinterventional coronary morphology is a significant factor in prognosis after interventional procedures and that the application of intravascular ultrasound can be useful in determining anatomic configuration, selecting treatment strategy, and defining optimal stenting strategies.

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Conclusions: Angiographic classification of LMCA bifurcation lesions is rarely accurate. Intravascular ultrasound shows that the carina is always spared and that the disease is diffuse rather than focal.3

Impact of Drug-Eluting Stents and Diabetes Mellitus in Patients With Coronary Bifurcation Lesions: A Survey From the Italian Society of Invasive Cardiology

Summary: The authors investigated the relationships between bare metal and drug-eluting stents according to the presence of diabetes mellitus (DM) among patients undergoing percutaneous coronary intervention of bifurcation lesions. At 3 years, compared with bare metal stents, stenting with drug-eluting stents was associated with lower adjusted risks of major adverse cardiac events, cardiac death, and target lesion revascularization in patients with DM. This benefit was not evident among patients without DM. These data suggest the beneficial effects of drug-eluting stents are most notable among patients with more complex types of coronary artery disease.

Conclusions: In a large observational registry with admitted potential for selection bias and residual confounding, drug-eluting stents in patients with DM with coronary bifurcation lesions were associated with improved outcomes in terms of MACE, cardiac death, and repeat revascularization at long-term follow-up. These figures were not replicated in non-DM subjects.4

Drug-Eluting Stents in Bifurcations: Bench Study of Strut Deformation and Coating Lesions

Summary: The side-branch ostium is the most common site for restenosis after drug-eluting stent (DES) deployment in coronary bifurcation lesions. The aim of the study was to analyze the consequences of the kissing postdilatation technique on 5 DESs, using microfocus x-ray CT and scanning electron microscopy. This bench test analysis suggests that when commercially available DESs are subjected to simultaneous kissing balloon postdilatation in an unconstrained model, elliptical deformation of the proximal segment, reduction of stent-to-artery ratio, and polymer coating damage at the side-branch ostium are observed. These DES changes may impair local drug delivery, thus limiting the effectiveness of these DESs and contributing to ostial side-branch restenosis. The results of the study could clarify restenosis mechanisms at the origin of the side branch in the case of kissing deployment of DESs and could lead to improving DESs or their use in clinical practice.

Conclusions: Commercially available DESs subjected to simultaneous kissing balloon postdilatation in an unconstrained model may contribute to side-branch ostial restenosis by proximal segment elliptic deformation and damage to the polymer coating.5

Anatomic and Functional Evaluation of Bifurcation Lesions Undergoing Percutaneous Coronary Intervention

Summary: To develop improved strategies and devices for coronary bifurcation lesions, better insight into both the anatomic and functional aspects of bifurcation lesions is required. The authors sought to investigate the mechanism of geometric changes after MB stent implantation and to identify the predictors of functionality significant jailed SB lesions with both intravascular ultrasound and fractional flow reserve. Intravascular ultrasound analyses showed that SB jailing can occur both by carina shift and plaque shift. Angiographic determinants of a functionally significant SB lesion were the preintervention SB percent diameter stenosis and the MB minimum lumen diameter located distal to the SB ostium, reflecting the degree of underlying disease and carina shift, respectively. However, it was difficult to predict the functional significance of each jailed SB lesion. This study showed the complex mechanism of SB jailing and its individual variability, which explains the difficulty of angiographic assessment in evaluating the functional significance of a jailed SB.

Conclusions: Both plaque shift from the MB and carina shift contribute to the creation/aggravation of an SB ostial lesion after MB stent implantation. Anatomic evaluation does not reliably predict the functional significance of a jailed SB stenosis.6

Changes in Left Main Bifurcation Geometry After a Single-Stent Crossover Technique: An Intravascular Ultrasound Study Using Direct Imaging of Both the Left Anterior Descending and the Left Circumflex Coronary Arteries Before and After Intervention

Summary: To assess geometric changes responsible for acute lumen loss at the left circumflex coronary artery (LCX) ostium after crossover stenting from the left anterior descending coronary artery to the left main artery, 23 left main bifurcation lesions with a preprocedural angiographic stenosis of <50% at the LCX ostium were evaluated by intravascular ultrasound. Both prestenting and poststenting pullbacks were used to calculate changes in minimal lumen area (MLA) within the LCX ostium (ΔL), external elastic membrane (EEM) area at the MLA site (ΔEEM), and plaque+media area at the MLA site (ΔP). The MLA within the LCX ostium significantly decreased from 5.4 mm² prestenting to 4.0 mm² poststenting (P<0.001). The percent change in MLA within the LCX ostium correlated with changes in EEM eccentricity at the LCX carina (r=-0.414, P=0.049) and percent change in EEM area at the MLA site (r=0.626, P=0.001). A smaller distal carina angle between the left anterior descending coronary artery and the LCX prestenting was associated with a greater percent reduction in lumen (r=0.472, P=0.023) and EEM (r=0.402, P=0.048) poststenting. In 18 lesions with >10% reduction of MLA within the LCX ostium, AP closely correlated with the ratio of ΔV to ΔL (r=-0.953, P<0.001), suggesting that an increase in plaque at the LCX ostium contributed to MLA loss relative to the decrease in EEM area.

Conclusions: Lumen loss at the LCX ostium frequently occurred after crossover stenting from the distal LM to the left anterior descending coronary artery. The main mechanism was carina shift, which was associated with a narrow angle between the left anterior descending coronary artery and LCX.7

Comprehensive Intravascular Ultrasound Assessment of Stent Area and Its Impact on Restenosis and Adverse Cardiac Events in 403 Patients With Unprotected Left Main Disease

Summary: Although proper stent expansion is essential to prevent drug-eluting stent restenosis and thrombosis, the lack of data for the left main (LM) and both side-branch ostia has limited the value of intravascular ultrasound optimization for LM stenting. A smaller minimal stent area predicted angiographic in-stent restenosis at 9 months after drug-eluting stent implantation to treat LM disease. The best minimal stent area criteria that predicted angiographic restenosis on a segmental basis were 5.0 mm² for the left circumflex artery ostium, 6.3 mm² for the left anterior descending artery ostium, 7.2 mm² for the polygon of confluence, and 8.2 mm² for the proximal LM above the polygon of confluence. Poststenting underexpansion was an independent predictor for 2-year major adverse cardiac events, especially repeat revascularization. With the criteria, intravascular ultrasound optimization during LM stenting procedures may improve clinical outcomes.

Conclusions: With these criteria, intravascular ultrasound optimization during left main coronary artery stenting procedures may improve clinical outcomes.8
Sirolimus-Eluting Stent Implantation for Ostial Left Anterior Descending Coronary Artery Lesions: 3-Year Outcome From the j-Cypher Registry

Summary: The ostial left anterior descending coronary artery (LAD) lesion is an important target for coronary revascularization because its location subtends a large territory of myocardium. However, percutaneous coronary intervention of the ostial LAD is often complicated by involvement of the distal left main coronary artery and potentially compromises the circumflex coronary artery. In this study, the long-term outcomes of sirolimus-eluting stent implantation for ostial LAD lesions were evaluated. Among 12,824 patients enrolled in the j-Cypher registry, 3-year outcomes were compared between 481 patients with sirolimus-eluting-stent–treated ostial LAD lesions and 5369 patients with sirolimus-eluting-stent–treated non-ostial proximal LAD lesions. Compared with patients with nonostial proximal LAD lesions, patients with ostial LAD lesions had similar incidences of target lesion revascularization and death or myocardial infarction. Among the patients with ostial LAD lesions, those undergoing both main- and side-branch stenting (n=62) compared with main-branch stenting alone (n=419) had a higher risk for target lesion revascularization but a similar risk for death or myocardial infarction. In patients with main-branch stenting alone, outcomes after crossover stenting of the circumflex coronary artery (n=225) were not different from those after ostial stenting (n=194) for both target lesion revascularization and death or myocardial infarction.

Conclusions: In terms of both safety and efficacy, 3-year outcomes of percutaneous coronary intervention using sirolimus-eluting stent for ostial LAD lesions were comparable to those for nonostial proximal LAD lesions. Crossover stenting with a 1-stent approach might be a reasonable option in treating ostial LAD lesions.

Randomized Trial of Simple Versus Complex Drug-Eluting Stenting for Bifurcation Lesions: The British Bifurcation Coronary Study: Old, New, and Evolving Strategies

Summary: Treatment of bifurcation coronary lesions generates much debate. The British Bifurcation Coronary Old, New, and Evolving strategies Trial recruited 500 patients with bifurcation lesions and randomly allocated them to either a simple strategy (main-vessel stenting with or without kissing balloon dilatation/T stenting) or a complex strategy (complete lesion coverage with either crush or cutolute stenting plus mandatory kissing balloon dilatation). Clinical follow-up of these 2 groups up to 9 months showed an 8% major adverse event rate in the simple group versus a 15% major adverse event rate in the complex group. This difference was largely driven by periprocedural myocardial infarction. The study therefore suggests that the usual strategy for the majority of bifurcation lesions should be the simple provisional strategy and that more complex strategies should be reserved for more complex anatomies, involving perhaps large side branches with significant length ostial side-branch disease.

Conclusions: When coronary bifurcation lesions are treated, a systematic 2-stent technique results in higher rates of in-hospital and 9-month major adverse cardiovascular events. This difference is largely driven by periprocedural myocardial infarction. Procedure duration is longer, and x-ray dose is higher. The provisional technique should remain the preferred strategy in the majority of cases.

Randomized Comparison of Final Kissing Balloon Dilatation Versus No Final Kissing Balloon Dilatation in Patients With Coronary Bifurcation Lesions Treated With Main-Vessel Stenting: The Nordic-Baltic Bifurcation Study III

Summary: The 1-stent bifurcation stenting approach with stenting of the main-vessel (MV) and optional side-branch stenting using drug-eluting stents is the preferred strategy to treat coronary bifurcation lesions. It is unknown whether a successful MV stenting procedure should be finalized by a simultaneous kissing balloon dilatation (FKBD). In the present study, 477 patients with successful MV stenting were randomized to FKBD versus no FKBD. The 6-month rates of major adverse cardiac events (cardiac death, non-procedure-related index lesion myocardial infarction, target lesion revascularization, or stent thrombosis) were similar and low in the study groups. FKBD reduced angiographic side-branch (re)stenosis, especially in patients with true bifurcation lesions. The simple no-FKBD procedures resulted in reduced use of contrast media and shorter procedure and fluoroscopy times. FKBD may be recommended in genuine bifurcation lesions treated with MV stenting but may be avoided in bifurcations without side-branch stenosis. Long-term data on stent thrombosis are needed.

Conclusions: MV stenting strategies with and without FKBD were associated with similar clinical outcomes. FKBD reduced angiographic side-branch (re)stenosis, especially in patients with true bifurcation lesions. The simple no-FKBD procedures resulted in reduced use of contrast media and shorter procedure and fluoroscopy times. Long-term data on stent thrombosis are needed.

Outcomes in Patients With De Novo Left Main Disease Treated With Either Percutaneous Coronary Intervention Using Paclitaxel-Eluting Stents or Coronary Artery Bypass Graft Treatment in the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) Trial

Summary: Contemporary consensus treatment guidelines continue to recommend coronary artery bypass grafting (CABG) as the gold standard for revascularization of unprotected left main (LM) stenosis but note that percutaneous coronary intervention (PCI) is feasible; for example, the American College of Cardiology/American Heart Association PCI guidelines recently upgraded LM PCI from a class III to class IIb (level B) recommendation. In the absence of a large, randomized, controlled trial, interventional cardiologists have had difficulty developing objective evidence-based criteria for determining the optimal revascularization strategy for a given patient. The Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial is the first large trial to randomize patients suitable for revascularization by either CABG or PCI using drug-eluting stents for the treatment of LM or 3-vessel disease. This article presents outcomes in the prespecified subgroup of patients (n=705) with LM disease. Patients with LM disease had comparable overall 12-month major adverse cardiovascular and cerebrovascular events in both the PCI and the CABG group (14% CABG versus 16% PCI). When patients were scored for anatomic complexity, those with higher baseline SYNTAX scores had significantly worse outcomes with PCI than those with low or intermediate SYNTAX scores; outcomes for patients with CABG did not correlate with baseline SYNTAX score. Thus, this short-term (1-year) analysis suggests that patients with LM disease who have low or intermediate SYNTAX scores may be safely treated with either PCI or CABG, but longer follow-up is needed.

Conclusions: Patients with LM disease who had revascularization with PCI had safety and efficacy outcomes comparable to CABG at 1 year; longer follow-up is required to determine whether these 2 revascularization strategies offer comparable medium-term outcomes in this group of complex patients.

In Vivo Wall Shear Stress Distribution in the Carotid Artery: Effect of Bifurcation Geometry, Internal Carotid Artery Stenosis, and Recanalization Therapy

Summary: These studies used flow-sensitive 4-dimensional MRI to analyze the in vivo distribution of wall shear stress in the carotid...
bifurcation and to evaluate its dependence on individual bifurcation geometry, the presence of internal carotid artery stenosis, and re-
canalization therapy. The size of the area of the normal carotid wall exposed to potentially hazardous wall parameters clearly correlated with markers for individual bifurcation geometry. The diameter ratio of the internal and common carotid artery, the bifurcation angle, and tortuosity may provide early predictors for regions prone to ather-
 sclerotic changes in the anatomic origin of wall parameters indicated that stenosis in the carotid bifurcation can result in the re-
 location of critical wall parameters to segments distal to the ather-
sclerotic lesion and that therapeutic intervention can result in similar wall parameter distribution as observed in healthy volunteers. Flow-
sensitive 4-dimensional MRI may become a valuable technique to assess the individual risk of flow-mediated atherosclerosis and car-
rotid plaque progression.

Conclusions: Flow-sensitive 4-dimensional MRI identified alterations in the segmental in vivo wall shear stress distribution associated with atherosclerotic disease, surgical therapy, and individual bifurcation geometry and could be a valuable technique to assess the individual risk of flow-mediated atherosclerosis and carotid plaque progression.13

Coronary Branch Steal: Experimental Validation and Clinical Implications of Interacting Stenosis in Branching Coronary Arteries

Summary: The literature indicates a profound disconnection among percent stenosis, coronary flow, patient selection for revasculariza-
tion, and failure of these procedures to reduce myocardial infarction or mortality in chronic coronary artery disease. It also documents poor correlation between coronary arteriographic severity and coro-
nary flow reserve caused by diffuse disease, arterial remodeling, endothe
lial dysfunction, and exertional sympathetic vasoconstriction. Failure of revascularization to reduce events or deaths in random-
ized trials may be because of the selection of patients on the basis of percent stenosis, which correlates poorly with coronary flow capac-
ity. In other randomized trials, revascularization based on fractional flow reserve has significantly better outcomes than revascularization based on arteriographic percent stenosis. This study adds insight to this disconnection by elucidating fluid dynamic interactions of mul-
tiple stenosis or diffuse disease in the branching coronary artery tree. The experimental model of proximal and distal stenosis separated by a nonstenotic arterial branch used in the study is a typical anatomic-
fluid dynamic subunit of coronary artery disease. Cumulative effects of these multiple subunits cause myocardial steal in the absence of occlusions and collaterals, hence the term branch steal. The data show that functional severity of anatomically fixed stenosis is not constant or independent of other stenosis or diffuse disease in the branching coronary tree. Given the anatomic complexity of coronary artery dis-
ease reiterated in this study, perhaps procedures designed to improve coronary flow should be based on quantitative coronary flow or my-
ocardial perfusion rather than simplistic flawed estimates of percent stenosis on arteriograms.14

Conclusions: Functional severity of anatomically fixed steno-
sis is not constant, specific, or independent of other stenosis in branching coronary arteries but requires analysis as an integrated component of the entire branching coronary artery tree to guide revascularizations.14

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