STATE-OF-THE-ART PAPER

Unprotected Left Main Intervention

Patient Selection, Operator Technique, and Clinical Outcomes

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In the 1980s, early attempts at balloon angioplasty of the unprotected left main coronary artery (UPLM) were associated with poor early outcomes because of coronary dissection, abrupt closure, and restenosis. Mortality rates as high as 30% at 1 year were reported. In the 1990s, bare-metal stents helped reduce acute complications, but high rates of repeat revascularization (20% to 30%) were observed because of restenosis. In the early 2000s, the introduction of drug-eluting stents (DES), with the promise of vastly reduced rates of restenosis, raised the possibility of improved late outcomes for UPLM patients receiving stents. Although use of DES for UPLM is currently a class III indication in patients who are candidates for coronary artery bypass graft (CABG), many patients are currently undergoing this procedure. Published registries indicate the procedural and in-hospital risks are acceptable and seem to be the same or lower than the procedural risks of CABG. Unprotected left main ostial and midshaft lesions have excellent early and midterm outcomes that will likely (although not yet proven) be similar to those of CABG. Distal left main lesions involving the bifurcation are technically more challenging and associated with a higher rate of late revascularization. Early registry data have not found excess mortality in patients receiving DES for UPLM when compared with historical bypass surgery data, even when the distal bifurcation is stented. However, current follow-up of stented patients is limited to 1 year or less. Over the next few years, the results of randomized trials will expand the evidence base available to clinicians caring for this challenging patient group. (J Am Coll Cardiol Intv 2008;1:5–13) © 2008 by the American College of Cardiology Foundation

The left main coronary artery's critical importance to coronary circulation has focused attention on this specific anatomical subgroup for decades. In the early 1970s, coronary artery bypass graft (CABG) was found to improve late survival in patients with significant left main stenosis in comparison with medical therapy (1–3). Once CABG became the standard of care for left main disease, a distinction between protected—by at least 1 patent bypass graft to the left coronary artery—and unprotected left main coronary arteries (UPLM)—no patent bypass graft to the left coronary artery—was

made. This review is confined to the treatment of UPLM disease. In the 1980s, early attempts at balloon angioplasty of the UPLM were associated with poor early outcomes because of coronary dissection, abrupt closure, and restenosis. Mortality rates as high as 30% at 1 year were reported (4–6). In the 1990s, bare-metal stents were introduced and soon were used to treat UPLM disease. Several small registries found a low rate of procedural complications, but rates of repeat revascularization of 20% to 30% because of restenosis were considered unacceptable (7–12). Early bare-metal stent registries for UPLM also found high mortality rates, particularly in high-risk patients, such as patients with acute coronary syndromes and poor left ventricular function. Importantly, high-risk subgroups often presented with late sudden death (11,13). In the early 2000s, the introduction of drug-eluting stents (DES), with the promise of

vastly reduced rates of restenosis (14–17), raised the possibility of improved late outcomes in this challenging patient group.

Early Clinical Results of DES for UPLM Stenosis

Clinical outcomes after treatment of UPLM disease with either the sirolimus-eluting stent (SES) or the paclitaxel-eluting stent (PES) from nearly 20 small registries have been published. Results reported in these registries vary widely (18–40). As depicted in Table 1, cardiac mortality between 6 and 12 months ranges from 0% to 11%. Target lesion revascularization (TLR) or target vessel revascularization (TVR) rates range from 2% to 38%. This wide variation in clinical outcome seems largely attributable to variation in both patient selection and procedural technique.

Although results after UPLM stenting are usually reported as a single, homogeneous subgroup of coronary artery disease, in reality, UPLM encompasses a wide spectrum of disease states. Outcomes will be particularly dependent on lesion location. Left main disease can be confined solely to the left main ostium or to the midshaft, regions technically not difficult to treat with a single stent, where excellent outcomes can be expected. In contradistinction, UPLM disease can be located distally, involving the ostium of the left anterior descending (LAD) and/or circumflex arteries, resulting in a much more technically complex procedure, often requiring double stenting, with expected less favorable long-term outcomes. Additionally, the UPLM vessel can be large in diameter and free of calcium, which is associated with better outcomes, or small in diameter and contain significant quantities of calcium,

Abbreviations and Acronyms

CABG = coronary artery bypass graft

DES = drug-eluting stent(s)

IVUS = intravascular ultrasound

LAD = left anterior descending artery

PES = paclitaxel-eluting stent(s)

SES = sirolimus-eluting stent(s)

TLR = target lesion revascularization

TVR = target vessel revascularization

UPLM = unprotected left main coronary artery

creating a technically demanding procedure that results in less favorable short-term and long-term outcomes.

Another important differentiating patient characteristic is the presence of significant distal disease in the LAD and/or circumflex arteries, requiring multilesion intervention. The presence of multiple downstream lesions will obviously increase procedural complexity and also increase the risk for subsequent revascularization. Finally, any study of UPLM must take patient comorbidity into consideration. Often, patients are refused CABG for UPLM disease because of serious comorbidities (i.e., stenting in the setting of acute myocardial infarction, advanced age, poor left ventricular function, coexisting malignancy, renal failure, and porcelain aorta) that will also impact long-term outcome after coronary stenting. Thus, published studies of UPLM stenting must be viewed in the context of the clinical, angiographic, and procedural (especially, number of stents needed) characteristics of patients enrolled in each specific study.

Figure 1 shows a patient with midshaft UPLM stenosis. This is one of the most straightforward UPLM lesions for stenting, and an excellent outcome was obtained after deployment of a single stent in the shaft of the left main artery. A recent multicenter registry of 147 patients (35) undergoing UPLM stenting of ostial or midshaft lesions with SES (n = 107) or PES (n = 40) found excellent results at midterm clinical follow-up (886 ± 308 days). In this registry, cardiac mortality was 0% in-hospital and 2.7% at follow-up. Cardiac mortality was 0% in 87 patients judged at low risk because of a EuroSCORE ≤6 and/or Parsonnet score ≤13 (41,42), but was 6.7% in 60 patients with high-risk scores. With over a 2-year mean follow-up in the entire group, TVR was only 4.7%. Thus, patients with ostial and midshaft UPLM lesions seem to have excellent outcomes after DES. These outcomes are likely to compare favorably with surgical outcomes, but we await the results of randomized trials before drawing conclusions.

In contradistinction to patients with ostial or midshaft lesions, patients with distal bifurcation lesions are more challenging to treat and have less favorable long-term outcomes. The initial Scripps Clinic UPLM experience

Table 1. DES for the Unprotected Left Main Coronary Artery							
	Park et al. (20)	Chieffo et al. (19)	Valgimigli et al. (37)	Lee et al. (28)	Price et al. (32)	Migliorini et al. (30)	Erglis et al. (38)
Patients, n	102	85	95	50	50	101	53
Distal lesion location (%)	71	81	65	60	94	87	81
Cardiac mortality, 6–12 months (%)	0	3.5	11	4	2	11	2
Angiographic follow-up (%)	84.3	NR	NR	42	98	96	100
Angiographic restenosis (%)	7*	19†	NR	NR	44‡	16*	6*
TLR or TVR (%)	2§	18.8‖	6.3‖	13‖	38§	14‖	2§

*Follow-up angiography at 6 months. †Follow-up angiography at 4 to 8 months. ‡Follow-up angiography at 3 and 9 months. §Target lesion revascularization (TLR). ‖Target vessel revascularization (TVR). Data from Baim et al. (39).
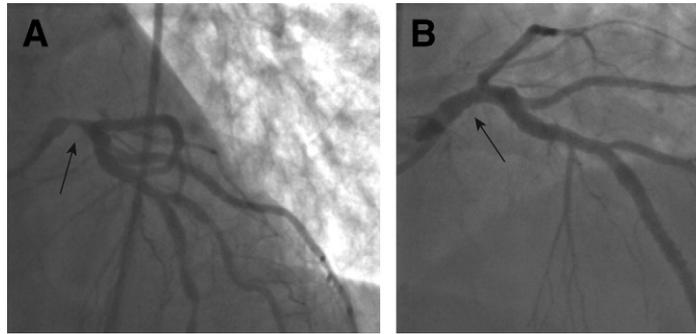
DES = drug-eluting stent; NR = not reported.

Figure 1. Critically Narrowed Midshaft Stenosis in an 83-Year-Old Man With Unstable Angina

This is one of the most straightforward unprotected left main coronary artery lesions for stenting **(A)**. The **arrow** shows the stenosis. Excellent angiographic outcomes were achieved after implantation of a single 8-mm-long drug-eluting stent, in addition to stenting of the mid left anterior descending artery **(B)**.

contained patients with predominantly distal bifurcation disease (32). In this small, 50-patient registry using SES for UPLM, 94% of patients had disease at the distal left main location. Instead of a single stent treating the left main and/or ostium of the LAD or circumflex artery, multiple stents were used in 84% of patients. This registry found a 9-month cardiac mortality rate of only 2%, but a TLR rate of 38%. Interestingly, the high TLR rate was also driven by an extremely high rate of angiographic follow-up. Fully 98% of patients had a follow-up angiogram at 3 and/or 9 months. Using an ischemia-driven TLR definition (patient has signs or symptoms of coronary ischemia), TLR was only observed in 14% of patients. This emphasizes the confounding impact of the occulostenotic reflex when interpreting results of UPLM stenting studies. Patients undergoing stenting of UPLM are often compliant with protocol-mandated surveillance angiography, and interventionalists are likely to have a low threshold to intervene when clinically silent restenosis is found in the left main vessel or the ostium of

the circumflex artery or LAD because of the large quantity of myocardial territory perceived at risk.

Interestingly, a universal finding of the many DES UPLM registries is the predominance of restenosis occurring at the ostium of the left circumflex artery, especially in patients initially presenting with distal bifurcation disease and treated with 2 stents. The cause of this restenosis predilection for the ostium of the circumflex is unknown, but may be attributable to the sharp bend often taken by the circumflex artery in this location, which could result in lack of stent and drug apposition to the vessel wall, or perhaps even stent fracture.

Figure 2 shows a relatively favorable UPLM distal bifurcation lesion. This 54-year-old patient with unstable angina has a lesion involving the distal left main vessel but very little involvement of the ostium of the circumflex artery. A single stent can be deployed from the distal left main vessel into the LAD crossing over the circumflex artery (the crossover technique). This lesion can be contrasted with the
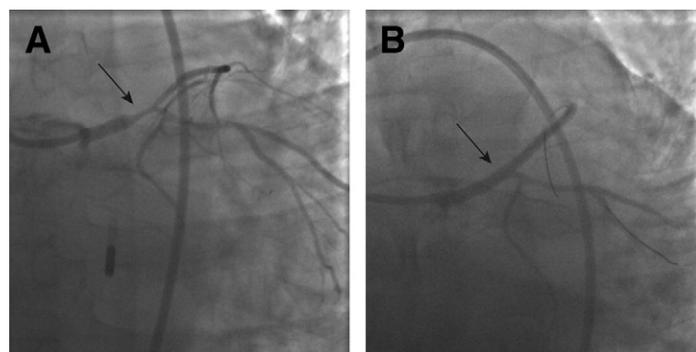

Figure 2. A 54-Year-Old Man With Favorable UPLM Distal Bifurcation Lesion

The lesion involves the distal left main vessel **(arrow)**, but there is very little involvement of the ostium of the circumflex **(A)**. A single stent was deployed from the distal left main vessel into the left anterior descending artery **(arrow)**, crossing over the circumflex artery (the crossover technique). Mild plaque shift into the circumflex was treated with a final kissing balloon inflation, providing an excellent angiographic result **(B)**. UPLM = unprotected left main coronary artery.
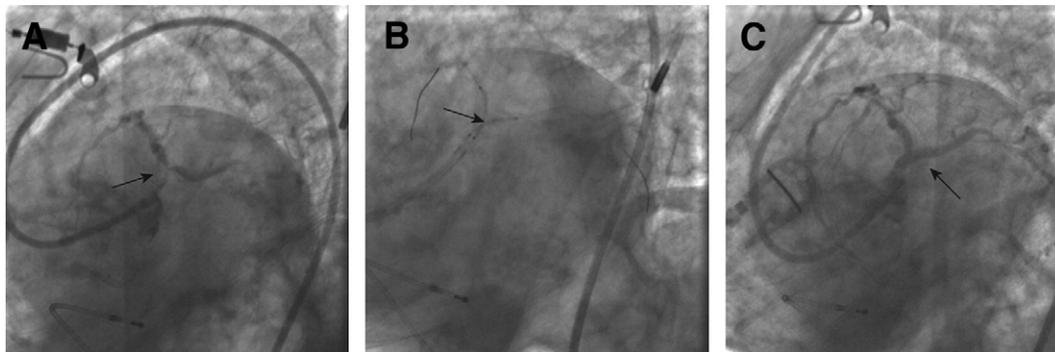
Figure 3. Pre-Procedure Angiogram From a 92-Year-Old Woman With Critical Aortic Stenosis in Preparation for Percutaneous Aortic Valve Implantation

This critically narrowed distal left main lesion **(A)** involves both the left anterior descending artery and circumflex ostia **(arrow)**. To reduce the risk of closing one of the branch vessels, 2 stents were deployed simultaneously **(arrow)** using the double-barrel technique **(B)**. The final angiographic result was excellent **(C)**, but this lesion is at higher risk for restenosis, particularly at the circumflex ostium **(arrow)**.

patient depicted in Figure 3. Here we see a highly stenotic, calcified UPLM lesion involving the distal left main and both left coronary branch ostia in a 92-year-old woman with concomitant critical aortic valve disease. This patient was considered at such high risk that an intra-aortic balloon pump was placed prophylactically and 2 stents spanning the left main vessel and each branch were simultaneously deployed (the double-barrel technique). This patient is at particularly high risk for restenosis, especially at the circumflex ostium.

There have been several small published registries comparing UPLM DES with CABG. Lee et al. (28) compared 173 consecutive patients at a single institution undergoing both procedures. The investigators found a nonsignificantly higher mortality rate at 6 months with CABG compared with DES (11% vs. 4%). Conversely, the rate of TVR was nonsignificantly higher in DES patients (7% vs. 1%). Similarly, Chieffo et al. (22) compared 107 DES to 142 CABG patients in a nonrandomized registry. At 1 year, death also trended higher in CABG patients (6.4% vs. 2.8%), and TVR was similarly higher in DES patients (19.6% vs. 3.6%).

Recently, a meta-analysis of 1,278 patients from 17 published studies undergoing DES for UPLM disease was reported (40). As previously highlighted, there was wide variation among trials with respect to baseline patient and angiographic characteristics. The overall midterm results (median follow-up was 10 months, range 6 to 19 months) found a mortality rate of 5.5% and TVR rate of 6.5%. Although these results are encouraging, it must be emphasized that there was substantial variation in outcome among these 17 trials (Figs. 4 and 5). The 5.5% pooled risk of late mortality reported in the meta-analysis may not apply to a specific patient in whom treatment options are being considered.

Patient Selection

Although numerous patients throughout the world are currently undergoing DES for UPLM, it should be emphasized that the current American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) Practice Guidelines for percutaneous coronary interventions clearly categorize UPLM stenting as a class III indication (43) (meaning it should not be undertaken) unless the patient is not a candidate for bypass surgery. However, the level of evidence provided is C (i.e., only consensus opinion of experts, case studies, or standard-of-care). Currently, without randomized trials, there is little evidence-based medicine available to guide patient care decisions. Therefore, the discussion that follows is the author's opinion based on consideration of available registry data and personal experience.

Before selecting a patient for UPLM intervention, one should be certain that left main disease exists. This is particularly important if a patient has an ostial main lesion evident angiographically only in the cranial angulation. This projection is notorious for artifactually enhancing the appearance of left main vessel stenoses. Intravascular ultrasound (IVUS) is the ideal method for confirming the presence of significant left main disease and also for guiding selection of stent size, assessing the presence of calcification, and documenting the involvement of the distal left main vessel and its branches. One commonly used IVUS threshold for significant left main disease is a minimal luminal area of <6.0 mm^2 (44); another is <7.5 mm^2 (45).

Informed consent is essential when considering patients for UPLM stenting. Patients who are not candidates for surgery because of comorbidities or poor distal targets are the least controversial to treat. These patients should be
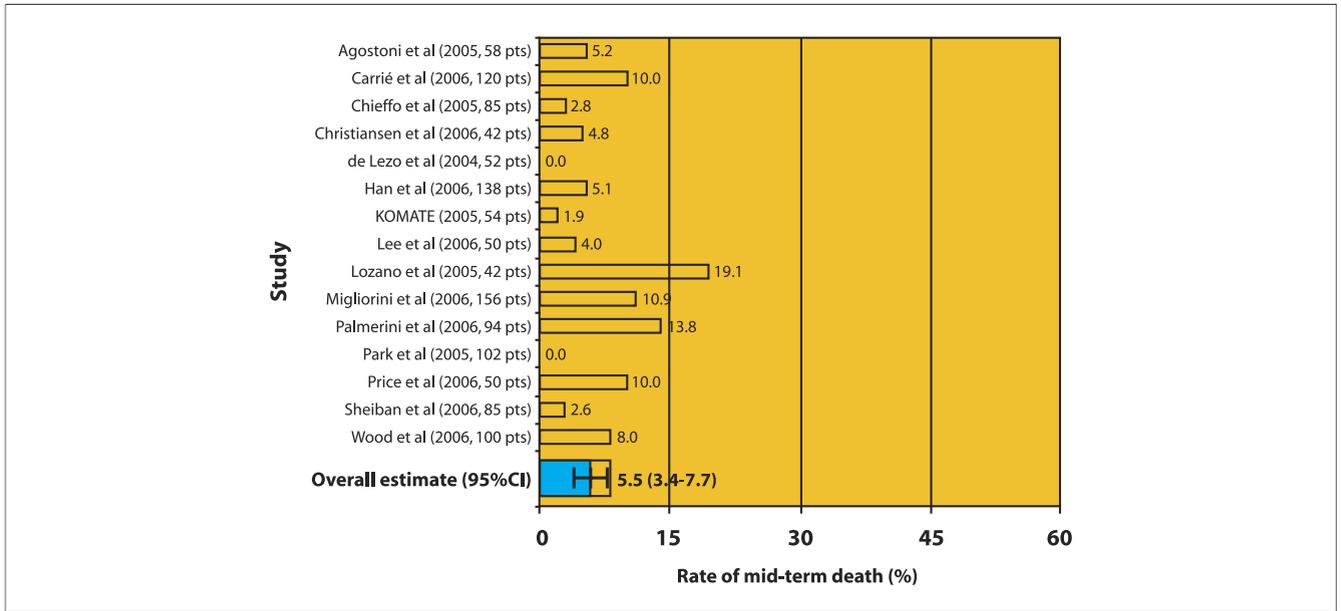
Figure 4. Recent Meta-Analysis of 1,278 Patients Undergoing UPLM DES From 15 Registries

At a median of 10 months of follow-up, the mortality risk was only 5.5% (range 3.4% to 7.7%). However, there was significant variation between registries, and the follow-up time was relatively short. Data from Biondi-Zoccai et al. (40). CI = confidence interval; DES = drug-eluting stents; UPLM = unprotected left main coronary artery.

informed that although stenting may be their best option, the long-term outcome after DES is, at present, poorly characterized. Patients who are acceptable candidates for CABG are extremely challenging to consent. Usually these patients request stenting instead of bypass surgery, with varying degrees of conviction. It is important to spend

considerable time with this patient group, going over the DES procedure and its potential risks and benefits in comparison with CABG. Ad-hoc stenting (46), wherein the patient gives consent while remaining on the catheterization table after the diagnostic examination, should be avoided. The importance of the UPLM artery should be graphically
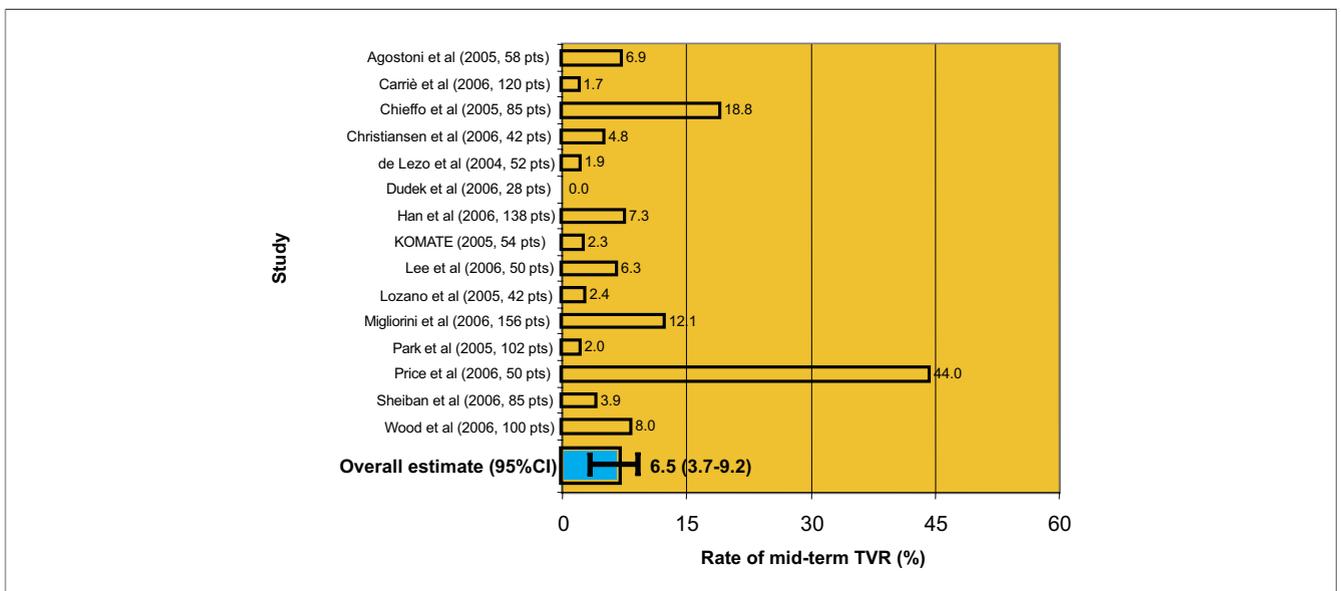

Figure 5. Recent Meta-Analysis of 1,278 Patients Undergoing UPLM DES From 15 Registries

At a median of 10 months of follow-up, the target vessel revascularization (TVR) risk was only 6.5% (range 3.7% to 9.2%). Note the extremely wide variation among the different registries. Data from Biondi-Zoccai et al. (40). Abbreviations as in Figure 4.

described to the patient. It is helpful to use an analogy, such as "the trunk of the tree," to visually emphasize the importance of this lesion's location. It is critical to make it very clear to the patient that UPLM stenting is not currently considered the standard-of-care by practice society guidelines and that the dataset we have regarding midterm and long-term outcomes is limited. It is often helpful to have a cardiovascular surgeon speak independently with the patient, as well as another cardiologist who is not an interventionalist. However, it is worth noting that having multiple physicians provide multiple opinions to a patient can also confuse some patients, upsetting them and making the decision process more difficult. The requirement for routine follow-up surveillance angiography must be explained and agreed to by the patient. Although some physicians do not believe routine surveillance angiography is warranted after UPLM stenting, this author strongly believes that follow-up angiography at 3 to 9 months is important, particularly in light of the limited data we have concerning late outcomes. Surveillance angiography after UPLM stenting is currently an ACC/AHA/SCAI Practice Guideline Class IIa (meaning it is favored) Recommendation (43).

One UPLM patient subgroup in whom DES might wisely be avoided are patients who have heavily calcified left main, ostial LAD, and/or circumflex coronary arteries and are otherwise good candidates for bypass surgery. These lesions are particularly challenging for percutaneous intervention and should be avoided even if a patient insists on DES. Finally, it should be noted that patients receiving DES for UPLM must be able to take dual antiplatelet therapy for a minimum of 12 months per current ACC/AHA/SCAI Practice Guidelines for DES (43). If possible, a longer duration of antiplatelet therapy may be advantageous.

Operator Technique

Left main ostial and midshaft lesions. Although ostial and midshaft left main vessel lesions are technically straightforward, there are some procedural caveats. Pre- and postprocedural IVUS is helpful for judging the degree of calcification, stent diameter selection, final stent expansion, and stent apposition, and for confirming the absence of stent edge dissection. In the U.S., the currently available SES can be expanded to 4.75 mm and the PES can be expanded to 4.25 mm. An intra-aortic balloon pump is rarely needed for ostial and midshaft lesions, but should be considered in patients who present with relative hypotension (i.e., systolic blood pressure <110 mm Hg), poor left ventricular function, and/or a totally occluded right coronary artery. Platelet glycoprotein IIb/IIIa inhibition should also be considered. Occasionally, a patient will have an extremely large diameter left main coronary vessel that is >4.75 mm. In these patients, in whom a DES of the necessary size is not available, consideration can be given to

implanting a large-diameter bare-metal stent. There are no data describing the outcome after large-diameter bare-metal stents in UPLM lesions. However, in other native vessel lesion locations, large-diameter bare-metal stents are associated with low restenosis rates. As with DES, surveillance angiography of a bare-metal stent is also extremely important.

Distal left main bifurcation involvement. Patients with distal left main disease involving the ostium of the LAD and/or circumflex artery are the most technically difficult to treat with stents. These patients often have significant coronary disease downstream from the left main vessel, which should be taken into consideration when making a decision between DES and CABG. When approaching these patients with DES, it is helpful to stent all of the downstream lesions first because stenting the left main vessel may make accessing the downstream lesions more difficult. In these patients, one should have a lower threshold for using an intra-aortic balloon pump, particularly if the systolic blood pressure is <110 mm Hg, the right coronary artery is occluded, left ventricular function is impaired, or the left main, LAD, and/or circumflex artery are significantly calcified. Heavily calcified UPLM arteries may require pre-treatment with rotational atherectomy, which increases procedural risk. These factors increase procedural risk and reduce long-term success and must be taken into consideration during the patient selection process.

From the available registry data, it seems that restenosis and repeat revascularization rates are profoundly lower if only 1 stent is used when treating the distal left main bifurcation (18–40). Provided the risk of closing the side branch is low, the currently favored technique is the provisional approach of stenting across the distal bifurcation, usually into the LAD. Often, the circumflex must be pre-dilated to avoid plaque shift and vessel shutdown with stent deployment. After stenting across the branch vessel, the branch will usually need to be rescued by recrossing with a guidewire and performing simultaneous kissing balloon inflation in both the stent and the branch vessel. Most interventionalists will perform a final kissing inflation even if the branch ostium is not compromised after stent implantation to widen the stent struts that cross the large branch vessel. Rarely, the ostium to the circumflex artery is heavily diseased with minimal disease of the LAD ostium, necessitating crossing over the LAD and stenting from the left main into the circumflex artery.

Deploying 2 stents in the distal left main vessel should be undertaken only when the operator strongly believes that the probability of acute closure of one of the branches is very high (i.e., the lesion shown in Figure 3). Faced with this situation, any 1 of the well-described double stent techniques (i.e., a double barrel, crush, T-stent, or modified T-stenting with intentional protrusion of the side-branch stent within the main vessel stent—TAP stenting) can be
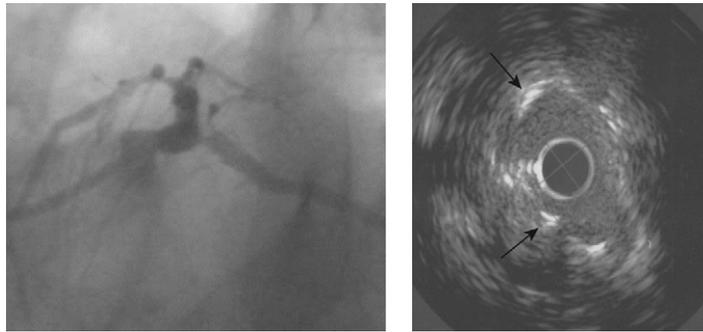
Figure 6. Bifurcation Stenting of a UPLM 5 Months Earlier

Follow-up angiography **(left)**, when viewed in the left anterior oblique and caudal projection, showed the appearance of an important stenosis at the circumflex ostium. However, intravascular ultrasound **(right)** showed no important stenosis and no neointimal hyperplasia, but instead, an eccentrically expanded stent **(arrows)**. The patient was asymptomatic with a fractional flow reserve after intracoronary adenosine of 0.92. This pseudostenosis in this asymptomatic patient was not treated. Image courtesy of Dr. Antonio Columbo, not previously published. UPLM = unprotected left main coronary artery.

used (47–59). When double stents are used, a final simultaneous inflation of both stents (kissing balloon inflation) at high pressure (>16 atm) with noncompliant balloons is considered critical to optimize outcomes. Whatever technique is chosen, a final examination using IVUS should be performed to ensure adequate stent expansion, complete stent strut apposition to the vessel wall, and absence of peri-stent dissection.

Surveillance angiography. Although controversial, this author believes 3- to 9-month surveillance angiography is important to rule out the possibility of restenosis presenting as sudden death. Although presently unproven, noninvasive surveillance with CT angiography may have a future role for the follow-up of UPLM stents. Unfortunately, routine surveillance angiography is likely to result in a higher rate of TVR; however, it seems prudent in light of our limited data regarding late mortality in this patient subgroup. When performing surveillance angiography, 1 caveat is to be aware of the potential for pseudostenosis at the ostium of the left circumflex artery. In patients treated with double stenting of a distal left main bifurcation, we and others have occasionally observed the angiographic appearance of a high-grade ostial circumflex stenosis that is not present when assessed with IVUS. This is likely because of the quantity of metal at the bifurcation, perhaps coupled with eccentric stent expansion (Fig. 6). It is important to use IVUS to rule out a pseudostenosis in this location and to avoid unnecessary repeat intervention, particularly in asymptomatic patients undergoing surveillance angiography.

When true in-stent restenosis of the unprotected left main vessel is observed at follow-up angiography, the results should be discussed with the patient in detail. If the patient is a candidate for CABG, the potential benefits and risks of CABG therapy versus percutaneous intervention should be once again explained. Usually left main in-stent restenosis is treated with repeat balloon angioplasty; stents are only added if the restenosis occurs at a stent margin. If repeat intervention is undertaken, further surveillance angiography is strongly recommended.

The future. At present, UPLM DES is controversial because there is so little scientific evidence to support it. Over the next several years, results of randomized trials comparing DES to CABG in this patient subset will become available. The SYNTAX (SYNergy Between Percutaneous Coronary Intervention With TAXus and Cardiac Surgery) trial has completed enrollment, and results should be available over the next 1 to 2 years. This large, randomized trial of surgery versus DES in patients with UPLM and/or 3-vessel disease has a pre-specified UPLM subgroup containing 710 randomized patients (60). This trial, along with other randomized trials, should provide important information, particularly with respect to comparative late mortality and the need for future revascularization. It will be important to analyze the results of these trials in the context of the lesion subtype (i.e., ostial, midshaft, and distal location) and the procedural stenting techniques used.

It should be noted that current DES technology has not been directed at UPLM intervention. If evidence accumulates indicating that this patient subgroup benefits from DES, dedicated UPLM DES technology will likely be developed. We are especially in need of a dedicated bifurcation DES stent with the dimensional requirements suited to the UPLM. For ostial and midshaft lesions, we are in need of a larger-diameter DES as well as a shorter-length DES, consistent with the dimensions of this vessel.

Conclusions

Although DES for UPLM is currently a class III indication in patients who are candidates for CABG, many patients are

currently undergoing this procedure. Published registries indicate the procedural and in-hospital risks are acceptable and probably the same or lower than the procedural risks of CABG. Unprotected left main ostial and midshaft lesions have excellent early and midterm outcomes that will likely (although yet unproven) be similar to those of CABG. Distal left main vessel lesions involving the bifurcation are technically more challenging and are associated with a higher rate of late revascularization. Surveillance angiography of patients undergoing UPLM DES, although not universally advocated, seems to be a reasonable method of minimizing the chance of a restenosis presenting as sudden death. There are many technical caveats to UPLM stenting. Improved technology, especially dedicated left main bifurcation stents, are needed. Early registry data have not found excess mortality in patients receiving DES for UPLM when compared with historical bypass surgery data. However, as yet, we have only early, 6-month to 1-year, follow-up of registry patients, and randomized trial results are not available. Over the next 1 to 2 years, the results of randomized trials will likely inform and transform the treatment of this important patient group.

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