# Drug-Eluting Stent Update 2007

## Part III: Technique and Unapproved/Unsettled Indications (Left Main, Bifurcations, Chronic Total Occlusions, Small Vessels and Long Lesions, Saphenous Vein Grafts, Acute Myocardial Infarctions, and Multivessel Disease)

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Randomized trials have largely demonstrated that percutaneous coronary intervention (PCI) with sirolimus-eluting (SES) and paclitaxel-eluting stents (PES) results in a significant reduction in the occurrence of angiographic restenosis and revascularization compared with bare metal stents (BMS).[1–4]

The benefit of drug-eluting stents (DES) also has been confirmed in "real-world" scenarios. In this setting, when the analysis was focused on high-risk patient and lesion subgroups, a benefit still existed despite the presence of restenosis.[5–7] These expanded indications do not yet cover many other types of complex lesions for which only registries or randomized trials, not yet published, are available so far (Tables 1 through 7). This topic is discussed in detail in this review. An important clarification is that the lack of proof is most probably due to the difficulty in performing randomized trials in high-risk groups using BMS as controls. It will be no surprise to find that the field in which DES perform best compared with BMS is likely to be complex lesions and patients[8] (Figure 1).

### Unprotected Left Main Coronary Artery

Current American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC) guidelines consider the presence of a stenosis in the unprotected left main coronary artery (LMCA) a class IIa or IIb indication, respectively, for PCI if coronary artery bypass grafting (CABG) is not a viable option.[9,10] Moreover, according to the AHA/ACC 2005 guidelines, in cases when the patient is eligible for CABG, PCI has a class III indication.[10]

Some retrospective studies evaluating surgical treatment for this disease reported an in-hospital mortality varying from 1.7% to 7.0% and a 1-year mortality of 6% to 14%.[11–14] Recently, encouraging results have been reported in some observational registries with elective DES implantation in LMCA, with a 1-year mortality of 0% to 5% in patients.[15–17] In these registries, the need for target lesion revascularization (TLR) varied from 0% to 14% and for target vessel revascularization (TVR) from 0% to 19%. In a registry in which all patients had contraindication to CABG and distal lesion location was present in 94% of the patients, TLR was 38% (14% if only ischemia-driven TLR is considered).[18] From these preliminary results, it is clear that patient selection and lesion location could be responsible for the differences in outcome reported in the different experiences.[19,20] Another important finding from these registries is the fact that in all of them, the major contributor to major adverse cardiac events (MACEs) is the need for a repeat procedure with no apparent increase in the incidence of myocardial infarction (MI) or death, albeit with the limitations of 1-year follow-up and a total of only 489 patients.

Most of the patients included in reports treating LMCA had distal stenosis requiring bifurcation treatment. The frequency of LMCA stenosis in the ostium and/or the shaft not involving the distal segment was 6% to 34%.[15,17,18,21] The presence of ostial and midshaft lesions in LMCA was associated with more favorable outcome with a low occurrence of restenosis (0% to 1%),[15,17,18,21] which was significantly higher for distal left main lesions,[22] especially with the 2-stent techniques.

More recently, 2 observational studies evaluating DES versus CABG have been reported.[16,23] Both studies found no difference in outcome between patients treated with stenting compared with those treated with CABG. The most important limitations of these registries are the fact that the 2 populations (PCI and CABG) had different baseline risk factors and that the follow-up was limited to 1 year.

At the present time, 2 randomized trials with extended follow-up to at least 5 years intend to evaluate the outcome of PES or SES versus CABG in patients with LMCA stenosis. The Synergy Between Percutaneous Intervention With TAXUS and Cardiac Surgery (the SYNTAX trial) will include 710 patients with LMCA lesions from a total cohort of 1800 patients with surgical disease. The Comparison of Bypass Surgery and Angioplasty (COMBAT) trial will evaluate only patients with unprotected LMCA. This study will include 1730 patients with LMCA randomized to SES versus CABG. The primary end point of the SYNTAX study is all major adverse cardiac and cerebrovascular adverse events,

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**TABLE 1. DES in Unprotected Left Main Stenosis**

| Study | n | Design | Distal Location % | Stent | Restenosis, % | TVR, % | Death, % |
|---|---|---|---|---|---|---|---|
| Park et al[17] | 102 | Case-control | 71 | SES/BMS | 7 | 2 | 0 |
| Chieffo et al[15] | 85 | Case-control | 81 | SES/PES/BMS | 19 | 18 | 3.5 |
| Valgimigli et al[21] | 95 | Case-control | 65 | SES/PES/BMS | Not reported | 6 | 14* |
| Price et al[18] | 50 | Case-control | 94 | SES/BMS | 42 | 38 | 2 |
| Lee et al[16] | 50 | Case-control | 60 | SES | Not reported | 13 | 4 |
| Chieffo et al[23] | 107 | Case-control | 81 | SES/PES | 17 | 15.8 | 2.8 |

*Includes patients with acute myocardial infarction.

including repeat revascularization at 1 year, whereas the COMBAT study has the composite of death, MI, and cerebrovascular events at 2 years as its primary end point.

While awaiting the results of the above studies, we think that the recommendations contained in the current guidelines are the most appropriate way to direct clinical practice in this patient subset.

## Bifurcation Lesions

Coronary bifurcations represent a challenging lesions subset and account for up to 15% of all current PCIs.[24] When contemplating a bifurcation lesion, one should bear in mind the size and territory of distribution of the side branch (SB) and the extent of disease in this vessel. In contemporary interventional practice, we cannot simplify treatment of bifurcations by omitting these initial considerations.

The introduction of DES has substantially improved the outcome in bifurcation lesions compared with BMS, resulting in lower adverse events and main branch (MB) restenosis rates. As a matter of fact, in the Arterial Revascularization Therapies Study II (ARTS-II), the subgroup of patients with bifurcation lesions treated with SES had the same incidence of 1-year MACEs as patients without bifurcation lesions.[25] One important feature of the ARTS-II study is that no prespecified angiographic follow-up was planned, a situation that is common to many studies evaluating provisional SB stenting.

Although provisional stenting technique (placing a second stent in the SB, after MB stenting, only in case of suboptimal or inadequate result) has remained the prevailing approach, several "2-stent techniques" have emerged ("crush") or been reintroduced (V, T, culotte, simultaneous kissing stents) to allow stenting in both branches when needed.[26]

The safety and efficacy of SES for the treatment of de novo true bifurcation lesions have been evaluated for the first time in a prospective multicenter study.[27] The 6-month total in-segment restenosis rate per lesion (the SB, MB, or both) was 25.7%, not significantly different between 2 stents (28.0%) and provisional SB treatment (18.7%) ($P=0.53$). Most restenosis occurred at the SB ostium and were focal. Because of the high rate of crossover, no conclusions could be drawn as to the most appropriate stenting technique. As in the Sirius bifurcation study,[27] no advantage was provided by provisional stenting in a study by Pan et al.[28]

The need for a technique able to provide full coverage of the SB ostium whenever the 2-stent approach is used prompted the development of the crush technique by our group.[29] The implementation of mandatory final kissing balloon inflation, not routinely performed in our preliminary experience, was done to correct stent deformation and to allow better strut contact against the ostium of the SB and therefore better drug delivery.[30] We have reported the long-term outcome of the crush technique after either SES or PES implantation in true bifurcation lesions accomplished with and without final kissing balloon inflation.[31,32] SB restenosis was significantly lower in the lesions treated with final kissing balloon compared with those without (11.1% versus 37.9%; $P\leq0.001$). Furthermore, whenever restenosis occurred, it was focal, located at the ostium of the SB (75.0%), and most of the time, it was not associated with symptoms or ischemia. An important technical aspect of the final dilatation is the performance of a high-pressure inflation at the SB ostium before the final kissing balloon inflation, which produces a better strut apposition on the wall of the SB.[33,34]

At the ACC meeting in Atlanta, Ga, in 2006, Steigen et al[35] presented 6-month results of the Nordic Bifurcation Study, which randomized 413 patients to stenting of both branches versus provisional stenting with SES. At 6 months, no difference existed between the 2 groups in terms of cardiac death, MI, index lesion MI, TVR, TLR, and stent thrombosis.

**TABLE 2. DES in Bifurcation Lesions**

| Study | n | Design | Stenting Technique | MB Restenosis, % | SB Restenosis, % | Restenosis/TLR, % Overall |
|---|---|---|---|---|---|---|
| Colombo et al[27] | 85 | Randomized | Both branches vs provisional stenting | 6.1 | 21.2 | 25.7/8.2 |
| Pan et al[28] | 95 | Randomized | Both branches vs provisional stenting | 6.2 | 10 | · · · / · · · |
| Ge et al[32] | 182 | Observational | Crush+FKB | 13.8 | 8.6 | Not reported |
| | | | vs T+FKB | 14.7 | 26.5 | |
| Hoye et al[33] | 231 | Observational | Crush | Not reported | Not reported | 25.3/9.7 |
| Moussa et al[34] | 120 | Observational | Crush | 2.6 | 7.8 | 11.3/11.3 |
| Steigen et al[35] | 413 | Randomized | Both branches vs provisional | · · · /1.4 (TLR) | Not reported | · · · /2.0 |

FKB indicates final kissing balloon inflation.

**TABLE 3. DES in Chronic Total Occlusions**

| Study | n | Design | Stent | Reocclusion, % | Restenosis, % | TLR, % |
|---|---|---|---|---|---|---|
| Hoye et al[41] | 56 | Observational | SES | 1.8 | 9.1 | 3.6 |
| Nakamura et al[42] | 60 | Prospective cohort | SES | 0 | 2 | 3 |
| Ge et al[40] | 122 | Observational | SES | 6.0 | 9.2 | 7.4 |
| Werner et al[44] | 48 | Observational | PES | 2.1 | 8.3 | 6.3 |
| Werner et al[45] | 61 | Observational | PES | 1.7 | 11.1 | 10 |
| Suttorp[46] | 200 | Randomized controlled | SES | 4 | 11 | 4 |
| de Lezo et al[47] | 118 | Randomized | SES/PES | 0 (SES) | 7.4 (SES) | 3.3 (SES) |
| | | | | 2 (PES) | 19 (PES) | 7 (PES) |

Important limitations of this study were the inclusion of nontrue bifurcations with a stenosis located only in the MB (true bifurcations have stenosis on the MB and SB) and the lack of systematic angiographic follow-up.

At the present time, it is not clear which is the better strategy, the provisional approach or stenting both branches, when dealing with a bifurcation lesion that has a stenosis in the SB suitable for stenting. Moreover, no study has yet addressed which is the best strategy to use among the several techniques reported in the literature when both branches are intentionally stented from the outset. Further information will come from the ongoing Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents (CACTUS) study. Despite the fact that no specific study has clearly demonstrated a specific higher risk of thrombosis of 2 stents versus 1 stent implanted in bifurcations, some reports raise some concerns about the higher thrombogenicity of 2 DES.[31,36,37]

Finally, an important issue is the emergence of dedicated stents, BMS or DES, for different types of bifurcations. These stents have specific designs intended to provide good deliverability, secure access to the SB, and complete coverage of the lesion site without double/triple layers of stent struts, thus incorporating the benefits of drug elution and ensuring drug availability to all diseased surfaces. While we await further data, our current approach to bifurcation lesions is summarized in Figure 2.

## Chronic Total Occlusion

Angiographic restenosis and reocclusion after BMS implantation in chronic total occlusion have been documented to occur in 32% to 55%[38,39] and 12%[39] of patients, respectively. As a result of these high restenosis rates after BMS implantation in chronic total occlusions, practice has therefore shifted to routine DES implantation in these lesions.

Both SES and PES have now been reported to be correlated with improved long-term clinical and angiographic outcomes compared with their BMS counterparts. Several studies reported the outcome after DES implantation in chronic total occlusion and compared the results to historical controls treated with BMS.[40–45] Overall, these studies reported single-digit restenosis rates after DES implantation without an increase in stent thrombosis or late occlusion (see Table 3).

The first randomized trial to compare SES (n=100) and BMS (n=100) was the Primary Stenting of Occluded Native Coronary Arteries (the PRISON II) study.[46] The primary end point of angiographic restenosis was significantly lower in the SES compared with the BMS group (11% versus 41%; $P<0.001$). The reocclusion rate also was lower in SES (4% versus 19%, respectively; $P<0.001$). Two cases of stent thrombosis occurred in the SES group but none in the BMS group.

Recently, a randomized study evaluating SES and PES has been presented.[47] No significant differences were reported between SES and PES in the rates of restenosis (7.4% versus 19%, respectively) and TLR (3.3% versus 7.0%). Death and MI rates were comparable between the 2 stents. Thus, emerging data suggest that DES may enhance long-term patency rates and freedom from restenosis and repeat revascularization compared with BMS in patients with chronic total occlusions.

## Small-Vessel Disease and Long Lesions

In general, most interventional cardiologists would agree that vessels <2.5 to 2.75 mm (by visual estimate) are considered small vessels. The most practical approach could be to qualify a small vessel as the one in which a stent with a diameter of ≤2.5 mm is going to be implanted. With an increase in the use of PCI as a revascularization option, interventions performed in small vessels are becoming more frequent, reach-

**TABLE 4. DES in Small-Vessel Disease and Long Lesions**

| Study | n | Design | Stent | Restenosis, % | TLR/TVR, % |
|---|---|---|---|---|---|
| Dawkins et al[5] | 219 | Randomized controlled | PES | 9.1 | 6.8/9.1 |
| Ardissino et al[51] | 129 | Randomized controlled | SES | 9.8 | 7/· · · |
| Mehilli et al[52] | 360 | Randomized controlled | SES vs PES | 11.4 vs 19.0 | 6.6 vs 14.7 |
| Aoki et al[54] | 122 | Observational | SES/PES | 5.3 | · · · /7 |
| Tsagalou et al[55] | 66 | Observational | SES/PES | 19.6 | · · · /15 |

**TABLE 5. DES in SVGs**

| Study | n | Design | Stent | TLR, % | MACEs, % |
|---|---|---|---|---|---|
| Ge et al[57] | 61 | Observational | SES/PES | 3.3 | 11.5 |
| Lee et al[58] | 139 | Observational | SES/PES | 10 | 10 |
| Hoye et al[59] | 19 | Observational | SES | 5 | 16 |
| Price et al[60] | 35 | Observational | SES | 6 | 31 |
| Tsuchida et al[61] | 40 | Observational | PES | 2.5 | 7.5 |
| Van Langenhove et al[63] | 311 | Randomized controlled | PES | 6.2 | 8.7 |

ing values as high as 67% in some reports.[48] Use of DES may further improve results in this high-risk subgroup.[49,50]

A randomized trial evaluating SES (n=129 patients) versus BMS (n=128 patients) in vessels with a reference diameter <2.75 mm has been conducted.[51] At 8 months, the primary end point of in-segment restenosis was detected in 9.8% of patients treated with SES versus 53.1% with BMS (relative risk, 0.18; 95% confidence interval [CI], 0.10 to 0.32; $P<0.001$). The superiority of SES compared with BMS also was observed in the occurrence of TLR (7% versus 21%; $P=0.002$) and MI (1.6% versus 7.8%; $P=0.04$).

A small randomized trial recently evaluated the efficacy of SES (n=180) versus PES (n=180) in small arteries (<2.80 mm by visual estimate). Angiographic restenosis was significantly lower with SES compared with PES (11.4% versus 19.0%; $P=0.047$), as was TLR (6.6% versus 14.7%; $P=0.008$).[52]

Even if not specifically designed as a small-vessel study, the Prospective, Randomized, Multi-Center Comparison of the Cypher Sirolimus-Eluting and the Taxus Paclitaxel-Eluting Stent Systems (REALITY) trial, which enrolled 1386 patients with an average reference vessel size of 2.40±0.48, can well be considered a small-vessel trial.[6] In this study, 701 patients were randomly assigned to receive an SES and 685 to receive a PES. The primary end point of in-lesion binary restenosis at 8 months occurred in 86 patients (9.6%) with an SES versus 95 (11.1%) with a PES (relative risk, 0.84; 95% CI, 0.61 to 1.17; $P=0.31$), with an in-stent late loss of 0.09 mm in SES versus 0.31 mm in PES (difference, −0.22 mm; 95% CI, −0.26 to −0.18 mm; $P<0.001$). No differences were detected in the occurrence of MACEs at 1 year (10.7% in SES versus 11.4% in PES; relative risk, 0.94; 95% CI, 0.69 to 1.27; $P=0.73$). Despite the encouraging results of DES implantation in small vessels, this subset of lesion is still one of the strongest predictor of restenosis.[53]

The use of PES versus BMS in long lesions has been evaluated in the TAXUS VI trial.[5] Four hundred forty-eight patients were randomized to moderate-release PES versus BMS. Mean lesion length in the study was 20.6 mm; the mean stent length was 33.4 mm. At 9 months, TVR was significantly lower in PES (9.1% versus 19.4%; $P=0.0027$; relative reduction, 53%), as was TLR (6.8% versus 18.9%, respectively; $P=0.0001$). The incidence of MACEs was similar in the 2 groups, 16.4% and 22.5%, respectively ($P=0.12$), including comparable rates for acute MI. Binary restenosis was reduced from 32.9% in the BMS group to 9.1% in the PES patients ($P<0.0001$).

Some registries report the experience of DES in very long lesions.[54,55] With the limitation that only 188 patients were included in these 2 studies, no concerns were present on the occurrence of stent thrombosis, with a major concern about a high incidence of non–Q-wave MIs due mostly to occlusion of small SBs.

Overall, we can state that the use of DES is advisable when treating small vessels. The value and the technique of using DES in long lesions are open to further analysis. The studies available still are not sufficient to establish definitive recommendations. We are not completely convinced that multiple long stents that cover the entire length of a major epicardial vessel, the so called "full metal jacket," represent the best long-term solution. Many problems are still on the table: the need for CABG limited by full-vessel stent coverage, the high incidence of periprocedural MI with long and multiple stents, and the risk of late thrombosis. With these limitations in mind, we should exercise some caution before fully suggesting this strategy.

## Saphenous Vein Grafts

PCI of saphenous vein grafts (SVGs) is associated with worse outcomes and a high incidence of in-stent restenosis.[56] The benefit of DES in this lesion subset has not been formally evaluated because SVG lesions have been excluded from randomized trials and the available data come only from observational studies. Moreover, the higher local prothrombotic conditions in SVG and the expected delay in endothelial healing after DES are claimed as possible drawbacks because

**TABLE 6. DES in Acute MI**

| Study | n | Design | Stent | Restenosis, % | TLR, % | MACEs, % |
|---|---|---|---|---|---|---|
| Lemos et al[67] | 186 | Observational Case control | SES/BMS | Not reported | 1.1 | 9.4 |
| Valgimigli et al[68] | 87 | Prospective cohort | SES/BMS | 9 | 5 | 18 |
| Spaulding[69] | 86 | Randomized controlled | PES/BMS | 5.9 | 3.7 | 5.9 |
| Dirksen et al[70] | 311 | Randomized controlled | PES/BMS | Not reported | 6.2 | 8.7 |
| Menichelli et al[71] | 320 | Randomized controlled | SES/BMS | 9.3 | 4.3 | 6.8 |

**TABLE 7. DES in Multivessel Disease**

| Study | n | Design | Stent | TLR, % | MACEs, % |
|---|---|---|---|---|---|
| Orlic et al[74] | 155 | Case series | SES | 14.3 | 22.3 |
| Briguori et al[75] | 100 | Case-control | SES/BMS | 8.0 | 25.0 |
| Serruys et al[76] | 607 | Non-randomized stratified | SES | 8.5 | 10.5 |

both can lead to higher rates of acute, subacute, and late thrombosis. Both SES and PES have been evaluated in small registries reporting low restenosis rates (≤10%) without any increased risk of stent thrombosis.[57–62]

At the ACC meeting in Atlanta, Ga, in 2006, the results of the Reduction of Restenosis in Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent (RRISC) trial were presented.[63] This trial is a prospective, randomized, double-blind study comparing SES and BMS in SVG lesions. The benefit of SES resulted in a restenosis rate of 11.4% in SES versus 30.6% in BMS ($P=0.02$).

Remaining issues are the long-term safety and efficacy of DES in SVG lesions, considering that long-term events frequently result from the progression of other lesions in the vein. Regardless of the future progress in this field, we think that DES treatment currently is the best approach for SVG lesions. We accept that this statement may be challenged by people who consider that many SVGs have reference vessels >3.5 mm in which a BMS may be as effective. We answer by stating that in most studies reporting restenosis rates after BMS implantation in SVGs, values >30% were found. Unless we see specific data on the outcome of BMS in very large SVGs, we maintain the proposed approach.

## ST-Elevation MI

Among all the unsettled or not fully tested indications for the use of DES, acute ST-elevation MI is most probably the one for which implantation of BMS remains the most used approach. The main reasons for this preference are the uncertainty about the thrombotic risk of DES in a thrombus-rich milieu and the low risk for restenosis after BMS implantation in patients with acute MI.[64–66] Despite these concerns, several recently published studies have addressed the safety and efficacy of DES implantation in the setting of primary PCI for acute MI. In fact, the PES has recently obtained approval in Europe for implantation in the setting of acute MI.

Lemos et al[67] have investigated the clinical impact of SES implantation in 186 patients undergoing primary angioplasty. Stent thrombosis did not occur in any patient in the SES group but in 1.6% of patients treated with BMS ($P=0.10$). At 300 days, treatment with SES significantly reduced the incidence of the composite of death, reinfarction, or TVR (9.4% versus 17%; hazard ratio, 0.52; 95% CI, 0.30 to 0.92; $P=0.02$).

In the Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent Versus Abciximab and Bare Metal Stent in Myocardial Infarction (STRATEGY) trial,[68] the cumulative incidence of death, reinfarction, stroke, or TVR at 8 months was significantly lower in the tirofiban and SES group compared with the abciximab and BMS group (18% versus 32%; $P=0.04$); the difference was due mostly to the reduction in the need for TVR.

Two randomized trials have been presented at the 2006 AAC meeting in Atlanta. In the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty (TYPHOON) trial,[69] 700 patients with acute MI were randomized to SES versus BMS. The primary end point of target vessel failure was significantly reduced in patients treated with SES compared with BMS (7.3% versus 14.3%; $P\leq0.001$) mostly because of the reduction in TVR (3.7% versus 12.6%; $P\leq0.001$). The occurrence of subacute thrombosis was no different between groups (3.4% in SES versus 3.6% in BMS).

Conversely, no differences in clinical outcome were detected in the Randomized Comparison of Paclitaxel Eluting Stent Versus Conventional Stent in STEMI (PASSION) trial.[70] In this study, 620 patients with acute MI presenting at 2 centers in the Netherlands were randomized to PES or

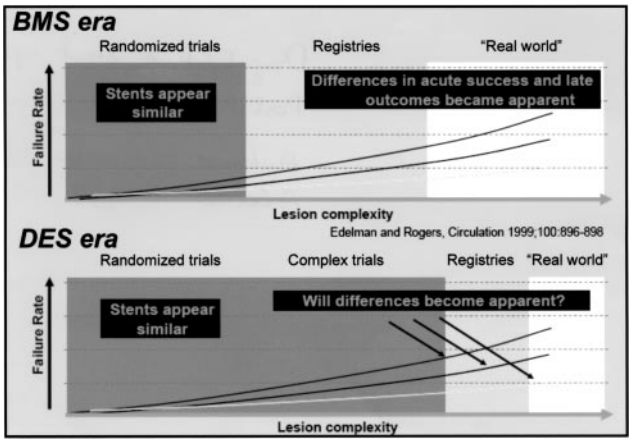


**Figure 1.** Lesion complexity and stent performance in the BMS and DES eras. Adapted from Edelman et al.[8]

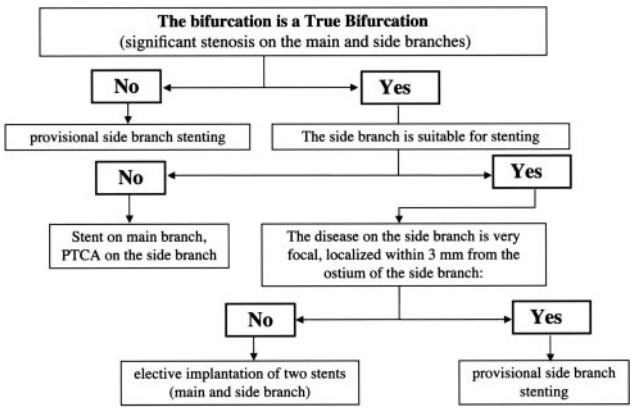


**Figure 2.** Current approach to bifurcation lesions in our center.

BMS. Angiographic follow-up was not mandatory. At 12 months, no significant difference was found in the occurrence of the primary end point of MACEs between the 2 study groups (8.7% in PES versus 12.6% in BMS; $P=0.23$). It is important to note that the MACE rate in the BMS group in TYPHOON was considerably higher compared with PASSION. The lack of mandated angiographic follow-up in the PASSION trial may have contributed to the lower incidence of events. Other differences in the 2 trials are that PASSION enrolled patients with left main disease, those with bifurcation lesions, and patients with a large thrombus burden, whereas TYPHOON specifically excluded these patients. Time from symptom onset to balloon inflation also was slightly longer in TYPHOON. Above all, it should be noted that TLR rates in the DES arms of both trials were similar.

At the Paris Course on Revascularization 2006, 12-month results from the Sirolimus-Eluting Stent in Acute Myocardial Infarction (SESAMI) were presented.[71] SESAMI is a single-center study from Rome (Italy) involving 423 patients with acute MI. Of these, 320 were randomized to treatment with either SES (n=160) or BMS (n=160). The 1-year angiographic results revealed binary restenosis rates of 9.3% for SES and 21.3% for BMS ($P<0.05$). The rate of TLR was 4.3% (SES) versus 11.2% (BMS), whereas the rate of TVR was 5.0% versus 13.1%. Overall MACE rates for SES and BMS were 6.8% and 16.8%, respectively ($P<0.05$; relative risk reduction, 59%).

The recent publication of the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) study reported a 9.0 hazard ratio of dying at 30 days in patients who stopped thienopyridine after DES implantation in the setting of acute MI.[72]

The ongoing Harmonizing Outcomes with Revascularization and Stents (HORIZONS) trial will randomize 3400 patients with acute MI undergoing primary angioplasty to PES versus BMS.

Therefore, results from currently published data with DES in acute MI are encouraging. Well-designed and appropriately powered clinical trials are warranted to establish long-term safety and efficacy (incremental advantage over BMS) of DES in this setting.

## Multivessel Disease

Compared with percutaneous transluminal coronary angioplasty with BMS implantation, CABG is associated with lower 5-year mortality, less angina, and fewer revascularization procedures.[73] The efficacy of DES in the prevention of restenosis suggests that this major limitation (resulting from the difference in revascularization rates) could finally be overcome.

Orlic et al[74] reported the outcome of 155 consecutive patients with 511 lesions treated with SES implantation ($3.3\pm1.3$ lesions per patient) in our center. At 6 months, the cumulative MACE rate was 22.3%. Cox regression analysis revealed total stent length per patient as the most powerful independent predictor of MACEs.

The impact of SES implantation on 12-month outcome in 100 diabetic patients with multivessel coronary artery disease has been evaluated by Briguori et al.[75] At 12 months, MACEs occurred in 25%, including a 17% need for reinterventions.

In the ARTS-II study,[76] a total of 607 patients treated with SES were enrolled in a registry with the intent to maintain the inclusion criteria of the ARTS-I randomized trial.[77] No difference existed in the MACE at 1 year between the ARTS-II DES registry patients and CABG randomized patients of the ARTS-I trial (10.4% versus 11.6%), and no difference existed in any other outcome. Recently, some concerns have been raised by the stent thrombosis rate in the patients treated with DES and included in the Argentine Randomized Trial of Coronary Stents Versus Bypass Surgery (ERACI III) Registry.[78] In the DES group, 7 patients (3.1%) experienced stent thrombosis; SES and PES had similar incidence (1.9% with SES and 1.5% with PES).

The ongoing SYNTAX trial will randomize 1800 patients with either left main or triple-vessel disease to receive either PES implantation or CABG. Two other ongoing randomized studies address the subset of diabetic patients with multivessel coronary artery disease. One, the United Kingdom– and Ireland-based Coronary Artery Revascularization in Diabetes (CARDia) trial, will enroll 600 patients with diabetes randomized to PCI with SES or to CABG. The primary end point in CARDia is a composite of death, MI, and cerebrovascular accident at 1 year. The other study is the National Health, Lung, and Blood Institute–sponsored Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multi-Vessel Disease (FREEDOM) trial, launched in April 2004. This study will randomize 2400 patients with diabetes and multivessel coronary disease to SES or PES versus CABG, with 5-year mortality as the primary end point.

Despite extensive real-life use of DES in patients with multivessel disease, we cannot deny that sufficient data are still lacking. Rather than looking at the incidence of new revascularizations, which may be considered an acceptable "side effect" (triggered by the tendency to perform repeat angiography in PCI patients and not in CABG patients) of any PCI strategy compared with CABG, we need to demonstrate equivalency or superiority in terms of MI and death evaluated no earlier than 5 years. In addition, the availability of large registries and sophisticated statistical techniques should not be used to draw premature conclusions[79] about a possible superiority of CABG versus DES in multivessel coronary disease.[80]

## Conclusions

DES have been widely adopted, and their use in the real world is in some cases beyond the indications evaluated in the randomized trials. In some subsets of lesions such as total occlusions, bifurcations, small vessels, long lesions, and SVGs, the data appear convincing enough to support extended applications. However, in other subsets such as patients with diabetes and multivessel disease, patients with unprotected left main disease, patients with triple-vessel coronary artery disease, and patients with acute MI, more data and longer follow-up are necessary before we can be confident enough to suggest the implantation of a DES as the default strategy. In addition, we can state that very low rates

of restenosis and revascularization and the lack of concerns about thrombosis reported in most randomized studies evaluating DES in approved indications are not always reproducible in most real-world patients. Finally, we cannot forget that results obtained with 1 type of DES should not be extended to any other DES.

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## Disclosures

None.

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KEY WORDS: angioplasty ■ coronary disease ■ myocardial infarction ■ restenosis ■ stents ■ thrombosis

# Drug-Eluting Stent Update 2007: Part III: Technique and Unapproved/Unsettled Indications (Left Main, Bifurcations, Chronic Total Occlusions, Small Vessels and Long Lesions, Saphenous Vein Grafts, Acute Myocardial Infarctions, and Multivessel Disease)

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