Treatment of Left Main and Multivessel Disease in the Drug-Eluting Stent Era

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For decades, the established standard of care for left main and multivessel coronary artery disease has been coronary artery bypass surgery because a significant survival advantage was found in patients revascularized with surgery compared with medical management. Although visions of less invasive strategies to manage this disease arose with the development of percutaneous coronary interventions, surgery proved to provide higher survival rates compared with balloon angioplasty and improved durability, with fewer required repeat revascularizations, compared with use of bare-metal stents. Drug-eluting stents revived hopes of an alternative treatment modality after trials demonstrated their safety and efficacy in other types of high-risk patients. Their widespread on- and off-label use led to several nonrandomized studies and, more recently, to randomized clinical trials comparing drug-eluting stents and bypass surgery.
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Clinical trials have established the safety and efficacy of drug-eluting stents (DES) in the treatment of low-risk, single coronary artery lesions.[1,2] Additionally, recent trials have demonstrated the effectiveness of DES in some high-risk populations, including patients across the entire spectrum of acute coronary syndromes.[3,4] These data have led to the widespread use of DES in more complex lesions, such as patients with left main or multivessel coronary disease, where coronary artery bypass grafting (CABG) surgery is the

recommended therapy according to current practice guidelines.[5] New data are now emerging to help guide clinicians as to the appropriateness of multivessel interventions with DES in these patient populations. This article reviews the history of left main and multivessel coronary artery disease treatment and discusses the role of DES.

The Pre-PCI Era

It has long been recognized that medically treated patients with left main coronary artery (LMCA) lesions have a poor prognosis compared with patients having lesions in other coronary arteries.[6] Registry data and randomized trials performed decades ago demonstrated that patients with LMCA lesions treated with CABG had improved long-term survival compared with patients who were treated with medical therapy.[7-9] The Veterans Administration Cooperative Randomized trial, the first randomized trial comparing medical therapy with CABG, found a 3-year survival advantage in LMCA patients undergoing revascularization with CABG compared with those treated medically.[8] These data were supported by an observational study that demonstrated improved 3-year survival in surgically treated patients compared with medically treated patients (91% vs 69%; $P < .0001$).[10] Furthermore, data emerged that CABG was a superior method of treating multivessel disease than medical management. The European Coronary Surgical Study (ECSS) found a long-term survival advantage in patients with 3-vessel disease and in patients with 2- or 3-vessel disease with a stenosis in the proximal third of the left anterior descending artery when randomized to CABG therapy (10.4% vs 18.5%).[9] Hence, surgery has been considered the gold standard therapy for LMCA lesions and multivessel coronary disease.

Balloon Angioplasty and Bare-Metal Stents for Left Main and Multivessel Disease Revascularization

The advent of percutaneous coronary interventions (PCI) offered the promise of less invasive therapy for coronary lesions; however, early results from balloon angioplasty in treating complex lesions were less than encouraging. In a reported series of 127 LMCA lesions treated with balloon angioplasty, cases were divided into 3 groups: elective protected cases, elective unprotected cases, and acute patients. At 3 years, mortality was 10% among patients with protected lesions, but it was 64% in patients with unprotected lesions and 70% in acute patients.[11] Thus, although PCI was possible for these lesions, surgical treatment of patients with LMCA disease was still preferred given the poor prognosis of unprotected or acute LMCA disease treated with angioplasty.[11,12] Balloon angioplasty of LMCA disease was reserved for patients who were not surgical candidates. Furthermore, the high rates of abrupt closure and restenosis of balloon angioplasty precluded its use in multivessel disease treatment.

The use of PCI was re-evaluated when bare-metal stents (BMS) were approved for de novo lesions and found to have improved outcomes by decreasing restenosis and abrupt closure rates compared with balloon angioplasty.[13] Although there were high rates of procedural success, there were also high rates of in-hospital and early posthospital discharge deaths.[14] In the Unprotected Left Main Trunk Investigation Multicenter Assessment (ULTIMA) registry, 107 patients underwent various percutaneous interventions (50% with BMS) for elective and acute treatment of LMCA disease. This registry reported a 10.6% rate of cardiac deaths among hospital survivors, presumably from abrupt closure, severe in-stent restenosis of the LMCA, or stent thrombosis.[14] The ULTIMA registry later reported on 279 patients with elective or emergent PCI for LMCA disease and found that at 1 year, all-cause deaths occurred in 24.2% of patients, cardiac deaths occurred in 20.2% of patients, and myocardial infarction (MI) occurred in 9.8% of patients.[15] Notably, low-risk patients in this registry (patients who were < 65 years old with LVEF $> 30\%$) had a mortality rate of 3.4%.[15] Thus, despite the feasibility and good immediate results of bare-metal stenting of LMCA lesions, the unacceptably high long-term complication rates, including restenosis and cardiac death rates, limited the widespread use of BMS in the treatment of LMCA disease.

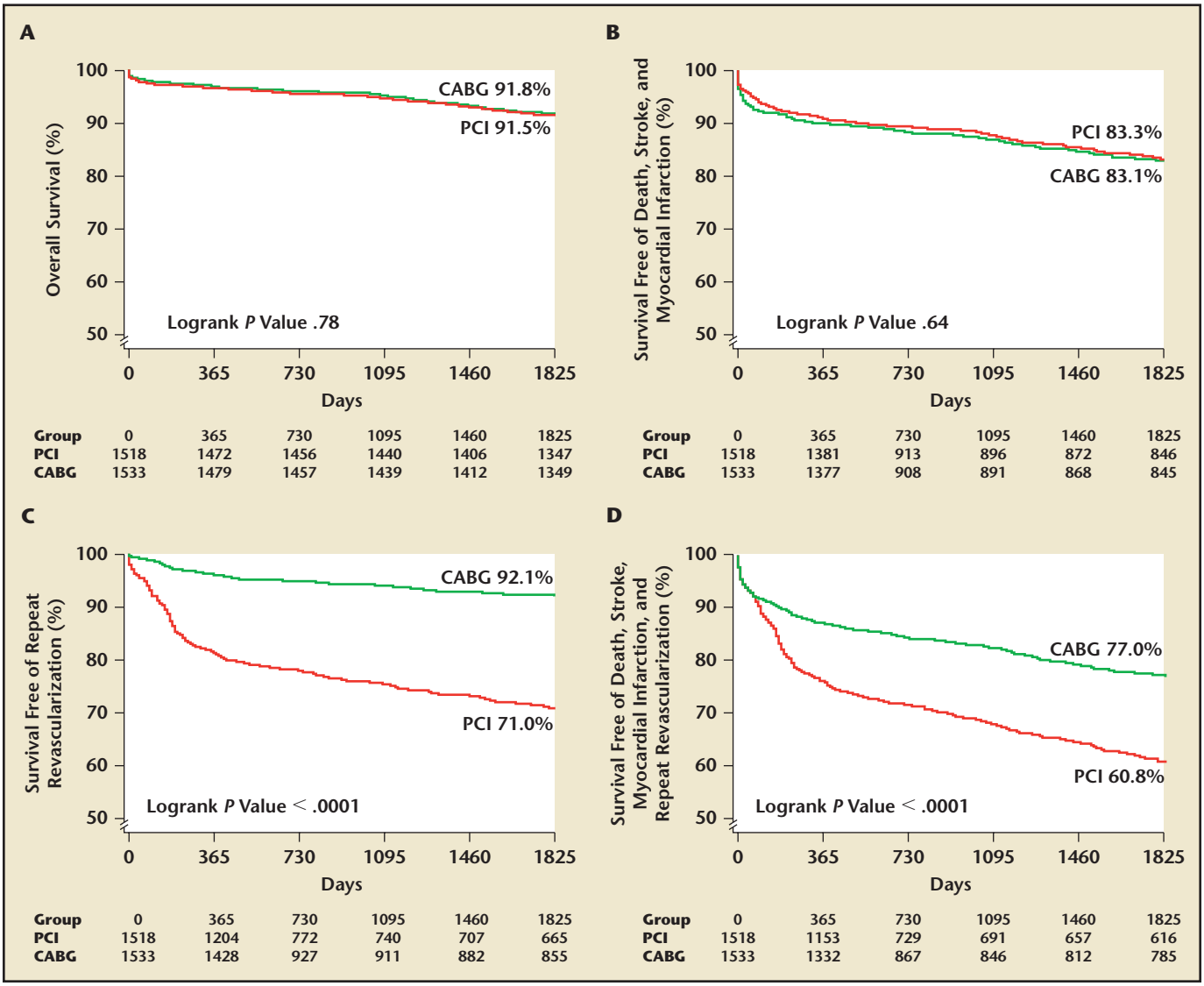
In the treatment of multivessel disease, observational studies found worse survival rates in patients receiving BMS compared with CABG.[16] To determine the role of BMS use in treating multivessel disease, 4 randomized trials (the Arterial Revascularization Therapies Study [ARTS],[17] the Argentine Randomized Trial of Coronary Angioplasty with Stenting Versus Coronary Bypass Surgery in Patients with Multiple Vessel Disease [ERACI II],[18] the Medicine, Angioplasty or Surgery Study [MASS II] for multivessel coronary artery disease,[19] and the Stent or Surgery [SoS] trial[20]) were performed, which produced conflicting results. Three of the trials showed no difference in the death rates between PCI with stenting and CABG at 5-year follow-up,[17-19] but the SoS trial demonstrated an improved 6-year survival rate in patients receiving CABG.[20] To more accurately gauge the efficacy of PCI with BMS in the treatment of multivessel disease, Daemen and associates[21] performed a patient-level pooled analysis of 3051 patients from these 4 randomized trials. In

this meta-analysis, the rates of the combined endpoint of death, stroke, or MI were similar between patients randomized to PCI with BMS or CABG at 5 years (16.7% vs 16.9%; $P = .69$). However, there were increased rates of repeat revascularization in the PCI group compared with the CABG group (29.0% vs 7.9%; $P < .001$), which led to an increased rate of overall major adverse cardiac and cerebrovascular events (MACCE) (defined as death, stroke, MI, and repeat revascularization) in the PCI arm versus the CABG arm (39.2% vs 23.0%; $P < .001$) (Figure 1).[21] Thus, despite similar survival rates between these 2 revascularization techniques, evidence favored CABG in providing a more durable therapy that required fewer repeat revascularization procedures.

Dawn of the DES Era

As PCI techniques evolved from BMS to DES, off-label use of DES has proliferated with the increasing use of DES in increasingly complex cases, including in the treatment of LMCA and multivessel disease. The development of DES reopened the debate on whether PCI could be used to treat these lesions. Because DES were shown to improve clinical

Figure 1. *Kaplan-Meier curves of event-free survival in CABG and PCI with BMS patients from patient-pooled analysis of the ARTS-I, ERACI-II, MASS-II, and SoS trials. Panel A: Event-free survival from death. Panel B: Event-free survival analysis from death, stroke, or myocardial infarction. Panel C: Event-free survival from repeat revascularization. Panel D: Event-free survival from major adverse cardiac and cerebrovascular events (death, stroke, myocardial infarction, and repeat revascularization). ARTS, Arterial Revascularization Therapies Study; BMS, bare-metal stents; CABG, coronary artery bypass grafting; ERACI-II Argentine Randomized Study: Coronary Angioplasty with Stenting Versus Coronary Bypass Surgery in Multi-Vessel Disease; MASS-II, Medicine, Angioplasty, or Surgery Study–II; PCI, percutaneous coronary intervention; SoS, Stent or Surgery. Reprinted with permission from Daemen J et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials.* Circulation. *2008;118(11):1146-1154.*[21]



outcomes and to specifically reduce restenosis and target lesion revascularization rates compared with BMS,[22-24] it was hoped that DES could be a more durable therapy that would narrow the gap in repeat revascularization rates between PCI and CABG and thereby improve MACCE rates.

In studies comparing the outcomes of patients treated with BMS to patients treated with DES for LMCA and multivessel coronary disease, patients who received DES had improved outcomes compared with those who received BMS.[25-27] In a retrospective study containing 220 patients, patients who were treated with DES had more multivessel and bifurcation disease than patients who received BMS. Nonetheless, after a mean follow-up of 15 months, major adverse cardiac event rates were significantly lower in the DES group than in the BMS group (9.5% vs 16.5%; $P = .029$). Furthermore, patients in the DES group had significantly lower rates of repeat revascularization procedures than patients in the BMS group (5.9% vs 11.6%; $P = .034$).[25] These results were consistent with those found in the ARTS-II trial, in which multivessel disease patients treated with DES were compared with historical BMS patients from the ARTS-I trial. This study found that ARTS-II DES patients had lower rates of MACCE—defined as all-cause death, MI, target vessel revascularization, or neurologic deficit—than ARTS-I BMS patients (81.0% vs 66.0%; $P < .001$) (Table 1).[27] Therefore, PCI with DES was a preferable technique over BMS in the treatment of these complex lesions, a finding that reinvigorated studies comparing PCI with CABG.

As for the data from the BMS versus CABG studies, there were conflicting results from trials comparing DES and CABG in the treatment of LMCA and multivessel disease. Some studies showed that DES and CABG revascularization had similar outcomes,[27-30] and others found that DES patients had poorer outcomes than CABG patients.[31] For example, in the ARTS-II trial, 607 patients with multivessel disease treated with sirolimus-eluting stents were compared with the historical CABG patients of the randomized ARTS-I trial. At 3 years, rates of MACCE were similar between ARTS-II DES patients and ARTS-I CABG patients (81% vs 83.8%; $P = .22$) (Table 1).[27] Thus, these studies suggested that PCI with DES could be the long-awaited less-invasive management alternative to CABG in the treatment of these high-risk lesions.

Although studies evaluating the role of DES in the treatment of LMCA and multivessel disease were encouraging, these reports were relatively small and often combined DES patients with BMS patients when evaluating the outcomes of PCI in comparison with CABG. Furthermore, some of these trials had strict inclusion/exclusion criteria and/or were not randomized. As a result, the data from these trials led to a growing need for a large, randomized controlled trial to re-evaluate how LMCA and multivessel disease should be treated, and once again challenged whether CABG should remain the gold-standard treatment.

Recently, Serruys and colleagues[32] reported a head-to-head comparison between PCI using DES versus CABG in treating LMCA and multivessel disease in the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. In this multicenter trial, eligible patients were enrolled if both a local interventional cardiologist and a cardiac surgeon determined that equivalent anatomic revascularization could be achieved via CABG or PCI with paclitaxel-eluting stents (TAXUS® Express®, Boston Scientific, Natick, MA). In contrast to prior studies comparing PCI and CABG, which contained strict inclusion and exclusion criteria and in which the latest techniques were not always used, SYNTAX used an all-comer approach and the newest techniques to mimic the real-life clinical setting. Patients with de novo LMCA (alone or in combination with 1-, 2-, or 3-vessel disease) or 3-vessel disease were prospectively randomized to either CABG or PCI in a 1:1 ratio. Randomization was stratified according to site, the presence or absence of LMCA disease, and medically treated diabetes.

Patients were treated with the intention of completely revascularizing all vessels at least 1.5 mm in diameter with stenosis of 50% or greater. Postprocedure medications were at the discretion of the individual sites. Patients receiving paclitaxel-eluting stents received antiplatelet therapy according to directions for TAXUS Express stent use and local practice. Most patients received thienopyridines for at least 6 months, with 71.1% of patients receiving them at 12 months. Aspirin was continued in all patients indefinitely.

The primary clinical endpoint of this trial was 1-year MACCE, defined as death from any cause, stroke, MI, or repeat revascularization. An independent clinical events committee adjudicated all primary clinical endpoints. Statistical analyses were performed with intention-to-treat populations and with as-treated populations.

Of the 4337 patients screened for this study, 1800 patients were randomized to receive either PCI with paclitaxel-eluting stents (903 patients) or CABG (897 patients). The 2 treatment arms were well matched

Table 1
The 3-Year Clinical Outcomes of ARTS-II Patients Receiving DES Versus Historical ARTS-I Patients Receiving BMS or CABG

	ARTS II N = 607 N (%)	ARTS I CABG N = 602 N (%)	ARTS I PCI N = 600 N (%)	ARTS II: I-CABG Difference (95% CI) (%)	ARTS II: I-PCI Difference (95% CI) (%)
Hierarchical					
Death	18 (3.0)	26 (4.3)	24 (4.0)	−1.4 (−3.5 to 0.8)	−1.0 (−3.1 to 1.0)
Cardiac	9 (1.5)	16 (2.7)	16 (2.7)	−1.2 (−2.8 to 0.4)	−1.2 (−2.8 to 0.4)
Noncardiac	9 (1.5)	10 (1.7)	8 (1.3)	−0.2 (−1.6 to 1.2)	0.1 (−1.2 to 1.5)
CVA	15 (2.5)	15 (2.5)	18 (3.0)	0.0 (−1.8 to 1.7)	−0.5 (−2.4 to 1.3)
MI	17 (2.8)	24 (4.0)	35 (5.8)	−1.2 (−3.2 to 0.9)	−3.0 (−5.3 to −0.7)
MI Q-wave	10 (1.6)	22 (3.7)	30 (5.0)	−2.0 (−3.8 to −0.2)	−3.4 (−5.4 to −1.3)
MI non–Q-wave	7 (1.2)	2 (0.3)	5 (0.8)	0.8 (−0.1 to 1.8)	−0.3 (−0.8 to 1.4)
Death/CVA/MI	50 (8.2)	65 (10.8)	77 (12.8)	2.6 (−5.9 to 0.7)	−4.6 (−8.1 to −1.1)
Revascularization	67 (11.0)	32 (5.3)	127 (21.2)	5.7 (2.7 to 8.8)	−10.1 (−14.2 to −6.0)
(re) CABG	13 (2.1)	5 (0.8)	40 (6.7)	1.3 (0.0 to 2.7)	−4.5 (−6.8 to −2.2)
(re) PTCA	54 (8.9)	27 (4.5)	87 (14.5)	4.4 (1.6 to 7.2)	−5.6 (−9.2 to −2.0)
Any MACCE	117 (19.3)	97 (16.1)	204 (34.0)	3.2 (−1.1 to 7.5)	−14.7 (−19.6 to −9.8)
Nonhierarchical					
CVA	17 (2.8)	19 (3.2)	20 (3.3)	−0.4 (−2.3 to 1.6)	−0.5 (−2.5 to 1.4)
MI	22 (3.6)	30 (5.0)	41 (6.8)	−1.4 (−3.6 to 0.9)	−3.2 (−5.8 to −0.7)
MI Q-wave	13 (2.1)	27 (4.5)	35 (5.8)	−2.3 (−4.4 to −0.3)	−3.7 (−5.9 to −1.5)
MI non–Q-wave	10 (1.6)	3 (0.5)	7 (1.2)	1.1 (0.0 to 2.3)	0.5 (−0.8 to 1.8)
Revascularization	87 (14.3)	39 (6.5)	158 (26.3)	7.9 (4.4 to 11.3)	−12.0 (−16.5 to −7.5)
(re) CABG	14 (2.3)	7 (1.2)	55 (9.2)	1.1 (−0.3 to 2.6)	−6.9 (−9.5 to −4.3)
–Target lesion	4 (0.7)	5 (0.8)	40 (6.7)	−0.2 (−1.1 to 0.8)	−6.0 (−8.1 to −3.9)
–Nontarget lesion	10 (1.6)	2 (0.3)	15 (2.5)	1.3 (0.2 to 2.4)	−0.9 (−2.5 to 0.8)
(re) PTCA	75 (12.4)	36 (6.0)	118 (19.7)	6.4 (3.1 to 9.6)	−7.3 (−11.4 to −3.2)
–Target lesion	48 (7.9)	22 (3.7)	86 (14.3)	4.3 (1.6 to 6.9)	−6.4 (−10.0 to −2.9)
–Nontarget lesion	37 (6.1)	15 (2.5)	42 (7.0)	3.6 (1.3 to 5.9)	−0.9 (−3.7 to 1.9)

ARTS, Arterial Revascularization Therapies Study; BMS, bare-metal stents; CABG, coronary artery bypass grafting; CI, confidence interval; CVA, cerebrovascular accident; DES, drug-eluting stents; MACCE, major adverse cardiac or cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty. Reprinted from *EuroIntervention* Volume 3, Serruys PW et al. Three-year follow-up of the ARTS-II–sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. Pages 450-459.[27] Copyright 2007 with permission from Europa Edition.

at baseline, except that the PCI group had higher rates of patients with blood pressures exceeding 130/80 mm Hg, and lower rates of smokers, patients with elevated triglycerides (≥ 150 mg/dL), and patients with decreased high-density lipoprotein levels (< 40 mg/dL for men or < 50 mg/dL for women). LMCA disease was present in 38.8% of CABG patients and 39.5% of PCI patients. On average, 4.4 lesions were treated per patient in the CABG arm and 4.3 lesions were treated per patient in the PCI arm. PCI patients received more postprocedural medications, including higher rates of antiplatelet medication usage.

In-hospital rates of MACCE were low in both the PCI (4.4%) and the CABG (5.4%) groups and were not significantly different (P = .31). At 1-year, the PCI arm had significantly higher rates of MACCE compared with the CABG arm (17.8% vs 12.4%; P = .002) (Figure 2). The per treatment analysis revealed similar results showing that patients who actually received PCI had significantly higher rates of MACCE compared with patients receiving CABG (17.6% vs 12.3%; P = .002). The increased MACCE rates in the PCI group were

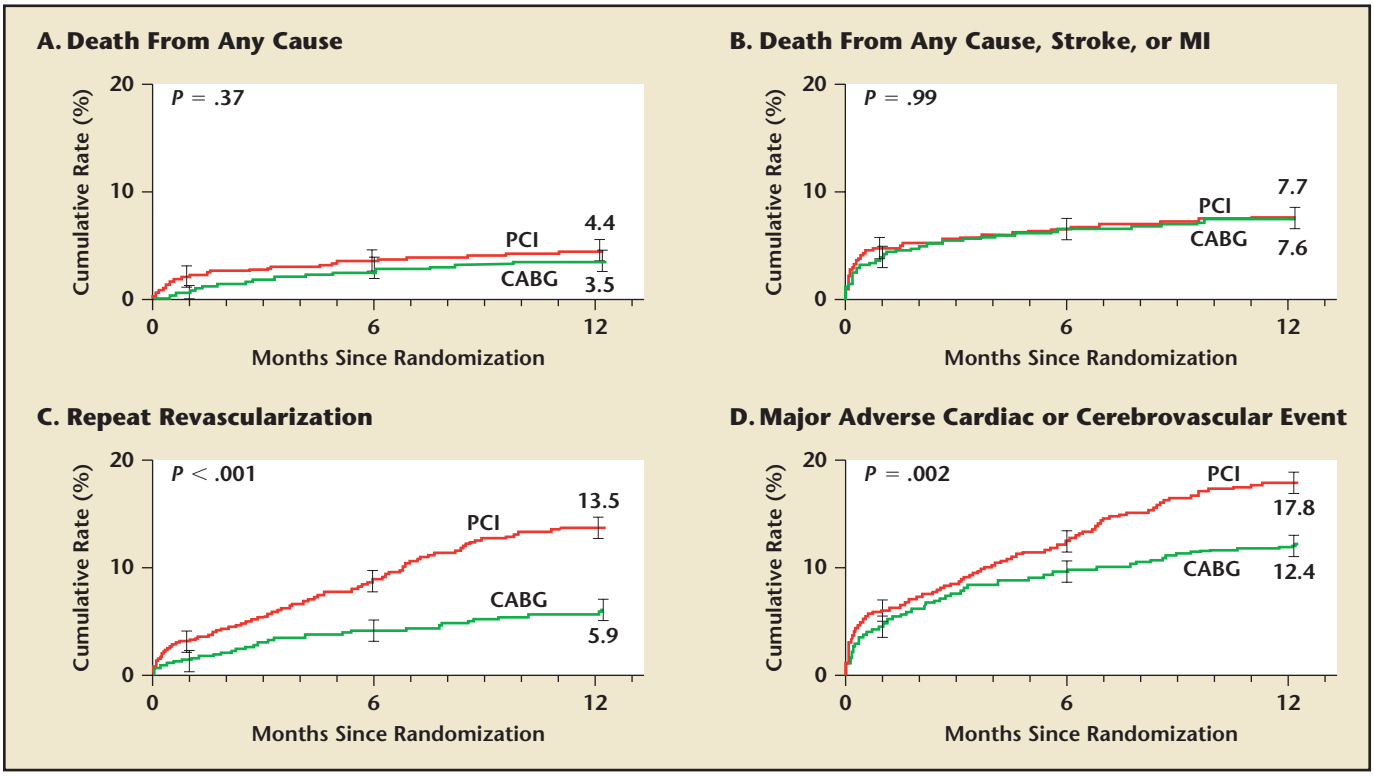


Figure 2. *Kaplan-Meier curves of event-free survival in CABG and PCI with DES patients from the SYNTAX trial. Panel A: Event-free survival from death from any cause. Panel B: Event-free survival from death, stroke, or MI. Panel C: Event-free survival from repeat revascularization. Panel D: Event-free survival from major adverse cardiac and cerebrovascular events (death, stroke, MI, and repeat revascularization). CABG, coronary artery bypass grafting; DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery. Reprinted with permission from Serruys PW et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease.* N Engl J Med. *2009;360:961-972.*[32] *Copyright © 2009 Massachusetts Medical Society. All rights reserved.*

primarily due to the PCI arm's higher rates of repeat revascularization compared with the CABG arm (13.5% vs 5.9%; $P < .0001$). Notably, among those patients who required repeat revascularization, most underwent another PCI procedure and not a CABG procedure. When the composite primary endpoint was broken into its individual components, patients in the PCI arm had similar rates of death from any cause, MI, and the combined endpoint of death from any cause, stroke, or MI compared with patients in the CABG arm. Furthermore, the 12-month rate of stent thrombosis in the PCI arm was similar to the rate of symptomatic graft occlusion in the CABG group (3.3% CABG vs 3.4% for PCI; $P = .89$). Patients receiving PCI had significantly fewer strokes (0.6% vs 2.2%; $P = .003$) than CABG patients.

Ong and colleagues[33] evaluated outcomes based on the complexity of the lesions according to the SYNTAX scoring system. An independent core laboratory scored each individual significant lesion according to the location of the lesion, adverse lesion characteristics, and the plaque anatomy at bifurcations. The sum of these individual SYNTAX coronary vascular complexity scores in a patient equaled the patient's general SYNTAX score.[33] Unlike CABG patients, who had similarly low rates of 1-year MACCE when divided into the low, intermediate, and high SYNTAX score groups (14.7% vs 12.0% vs 10.9%), patients in the PCI group had significantly higher rates of MACCE when they had high SYNTAX scores (23.4%) as compared with PCI patients in either the low (13.6%; $P = .002$) or intermediate (16.7%; $P = .04$) score groups. A significant SYNTAX score and treatment group interaction was found ($P = .01$). CABG and PCI patients with low or intermediate SYNTAX scores had similar MACCE rates, but PCI patients with high SYNTAX scores had significantly higher MACCE rates compared with CABG patients with high SYNTAX scores (23.4% vs 10.9%; $P < .001$).

Given the trial's results that CABG patients had improved 1-year MACCE rates compared with DES patients, the study concluded that CABG should remain the standard of

care treatment of patients with 3-vessel or LMCA disease. However, there are important nuances to the results of this trial. Although CABG patients had lower 1-year MACCE rates, this was predominantly based on a decreased rate of repeat revascularization in this group that did not translate into increased rates of overall deaths or MIs. Furthermore, PCI patients who required repeat revascularization mostly underwent another PCI procedure and did not require an invasive CABG surgery. Compared with CABG patients, PCI patients benefited from decreased rates of stroke at 1 year; however, it is unclear whether these improved rates were in part a result of increased dual-antiplatelet therapy usage in PCI patients or heightened postoperative stroke risk. Thus, the potential harm of increased revascularization rates must be weighed against the invasiveness of CABG surgeries and the possible morbidity of strokes when deciding the care plans of individual patients.

The SYNTAX trial provided additional data to help guide clinicians as to which patients are less likely to benefit from a PCI procedure. Using the SYNTAX scoring system, PCI patients with high SYNTAX scores had significantly worse MACCE rates compared with PCI patients with low or intermediate scores and compared with CABG patients who also had high SYNTAX scores. The ability of the SYNTAX score to predict MACCE outcomes in patients undergoing PCI for 3-vessel disease was consistent with a retrospective analysis of the ARTS-II trial with data regarding 1292 lesions in 306 patients receiving a sirolimus-eluting stent (CYPHER®, Cordis, Warren, NJ).[34] After a median follow-up of 370 days, patients in the highest SYNTAX score tertile had significantly higher MACCE rates (27.9%) than patients in the lowest tertile (8.7%; $P = .001$) or patients in the 2 lowest tertiles combined (9.9%; $P = .0001$). Similar results to the SYNTAX study were also seen in a small cohort study of 320 patients, in which patients undergoing CABG for 3-vessel disease had similar 1-year outcomes irrespective of their SYNTAX score.[35] Thus, PCI procedures should not be performed in the patient population with high SYNTAX scores.

The subset of SYNTAX patients with left main CAD (348 patients undergoing CABG and 357 patients undergoing TAXUS) was heterogeneous, with 13% having isolated left main (LM) disease, 20% with 1-vessel CAD, 31% with 2-vessel CAD, and 37% with 3-vessel CAD. In the LM cohort, the overall 12-month safety endpoint of death/MI/cerebrovascular accident was similar with both revascularization strategies (9.1% CABG vs 7.0% TAXUS; $P = .29$), as was the overall safety and efficacy endpoint of MACCE (13.6% for CABG vs 15.8% for TAXUS; $P = .44$). In further subset analysis, patients with isolated LM (n = 91) and LM with 1-vessel CAD (n = 138) had favorable MACCE rates with PCI compared with CABG (7.1% TAXUS vs 8.5% CABG in isolated LM and 7.5% TAXUS vs 13.2% CABG in LM with 1-vessel CAD), suggesting that PCI with DES does have a role in select lower-risk LM patients.[36]

The SYNTAX trial responded to the need for a large randomized trial studying contemporary techniques of revascularization in patients with complex multivessel and LMCA disease. However, additional questions remain. Further studies are needed to elucidate differences in the individual component endpoints and patient subsets, as SYNTAX was not powered to definitively draw conclusions for patient subsets, such as those with LM disease, that were only hypothesis-generating. Therefore, further studies are needed to establish the role of contemporary PCI with DES in different patient populations, such as those with left main disease or diabetes.

Several other recent studies have examined the use of DES in left main disease. The Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization (MAIN-COMPARE) study evaluated long-term clinical outcomes in 858 patients with unprotected LMCA disease who received a sirolimus-eluting stent (n = 669) or a paclitaxel-eluting stent (n = 189).[37] After 3 years of follow-up, both groups of patients had similar long-term clinical outcomes in terms of death, MI, repeat revascularization, and stent thrombosis. The adjusted risk of death, MI, or target vessel revascularization was 25.8% in the sirolimus-eluting stent group and 25.7% in the paclitaxel-eluting stent group. In the Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions (ISAR–LEFT MAIN) study, patients who received a sirolimus-eluting stent (n = 305) or a paclitaxel-eluting stent (n = 302) had similar rates of death, myocardial infarction, and target vessel revascularization.[38] The Left Main Coronary Artery Stenting (LE MANS) study compared rates of early and late outcomes of unprotected left main coronary artery disease in patients who received a BMS or a DES. The DES patients had a significantly lower rate of major adverse coronary artery events (25.9% vs 14.9%; $P = .039$).[39]

Revascularization in the Diabetic Patient With Multivessel Coronary Artery Disease

The optimal revascularization strategy for diabetic patients with multivessel coronary artery disease remains controversial. The original Bypass Angioplasty Revascularization Investigation (BARI) trial demonstrated that although the overall survival of patients in the study was similar, survival among diabetic patients was significantly worse with PCI compared with CABG (55.7% PCI vs 76.4% with CABG) at 7 years.[40] However, the outcomes of patients with diabetes were similar in the BARI registry when the selection of the revascularization strategy was left to the physician.[41] Ultimately, data from BARI are outdated because the strategies and techniques of both CABG and PCI have since dramatically evolved, but the results underscore the importance of applying clinical judgment in selecting the optimal revascularization strategy. The recent Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial demonstrated the selection of a more complex patient subset with greater coronary disease burden for bypass surgery rather than PCI when the decision is left to the treating physician.[42] BARI 2D suggested that in appropriately selected patients, there is an important role for revascularization with either PCI or CABG, with a greater proportion of patients deemed appropriate for PCI (68%) compared with CABG (32%). Beyond the extent of CAD disease burden, the selection of patients in the CABG stratum was driven by the perceived likelihood of success and procedure safety.

A recent meta-analysis included 499 patients with diabetes from 6 randomized trials: Angina With Extremely Serious Operative Mortality Evaluation (AWESOME), BARI, Emory Angioplasty versus Surgery Trial (EAST), ERACI II, MASS II, and Randomised Intervention Treatment of Angina (RITA). It demonstrated that the 5-year mortality was not significantly different between patients who received CABG or BMS (19.3% vs 17.3%; P = NS). The Coronary Artery Revascularization in Diabetes (CARDIA) trial was a randomized trial that enrolled 245 diabetic patients to CABG and 251 patients to PCI, with DES in 71% of cases.[43] The primary endpoint of MACCE (death, MI, revascularization, and stroke) favored CABG compared with stent implantation (11% vs 17.5%; P = .04), with a trend for fewer strokes with PCI (0.4% vs 2.5%; P = .09). Among the cohort of patients treated with a DES, MACCE rates were similar (11% for CABG vs 15.1% for DES), and stroke was significantly lower in the DES group (2.5% vs 0%; P = .04). In the SYNTAX trial, 452 patients with medically-treated diabetes and LMCA or multivessel coronary artery disease were randomly assigned to either CABG (n = 221) or PCI with TAXUS (n = 231).[44] Although death (all-cause) to 12 months was increased in patients with diabetes (vs patients without diabetes) treated with either CABG or TAXUS, the requirement for repeat revascularization was increased following TAXUS (11.1% in nondiabetic subjects vs 20.3% in diabetic subjects; $P < .001$) but not CABG (5.7% in nondiabetic subjects vs 6.4% in diabetic subjects; P = .74). Among diabetes patients, both the rates of revascularization and death (all-cause) to 1 year increased by SYNTAX score tertile following TAXUS PCI but not CABG. Thus, the angiographic lesion complexity score directly influenced clinical outcomes to 1 year following TAXUS PCI but not CABG. The relative advantage of CABG revascularization (vs PCI) was most evident among insulin-dependent diabetes patients and in patients with more complex angiographic lesion morphology. The ongoing FREEDOM trial is a 1:1 randomized study comparing the outcome of PCI with DES versus CABG among 2400 patients with diabetes and multivessel coronary artery disease (left main acute MI and shock excluded). The primary endpoint is a composite of death, MI, and stroke at 3 years. Enrollment completion is anticipated in mid-2009. The FREEDOM trial will be the definitive trial to establish the optimal revascularization strategy in this patient population using contemporary therapies and techniques.

Conclusion

For nearly 3 decades, CABG has been considered the standard of care therapy for LMCA and multivessel coronary artery disease after early studies showed its survival benefit compared with medical therapy alone. With the evolution of PCI over the last 2 decades, the opportunity for a lesser invasive revascularization alternative has become a reality for certain patient subsets. Most recently, DES has reduced repeat revascularization rates and improved survival rates compared with BMS in patients requiring coronary revascularization. Although contemporary studies continue to demonstrate that CABG provides more durable revascularization of LMCA and multivessel coronary disease with lower revascularization rates, this finding is offset by increased morbidity related to cerebrovascular events. Furthermore, contemporary trials do provide insight into risk stratification of those higher risk patients (those with

high SYNTAX scores and high disease burden) who benefit the most from CABG and lower risk patients (those with low and intermediate SYNTAX scores and isolated left main disease) who can be safely treated with PCI and DES to reduce the risk of morbidity associated with CABG. Results from the ongoing FREEDOM trial and additional future trials will be required to establish the role of PCI in particular patient subsets, such as those with left main disease. Until such studies are completed, DES remain off-label in these complex patient subsets. ■

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Main Points

- It has long been recognized that medically treated patients with left main coronary artery (LMCA) lesions have a poor prognosis compared with patients with lesions in other coronary arteries.
- Despite similar survival rates between bare-metal stents (BMS) and coronary artery bypass graft (CABG) surgery, evidence favored CABG in providing a more durable therapy that required fewer repeat revascularization procedures.
- In studies comparing the outcomes of patients treated with BMS to patients treated with drug-eluting stents (DES) for LMCA and multivessel coronary disease, patients who received DES had improved outcomes compared with those who received BMS.
- Results from the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial suggested that CABG should remain the standard of care treatment of patients with 3-vessel or LMCA disease, but that percutaneous coronary intervention (PCI) with DES has a role in select lower-risk LMCA patients.
- The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial suggested that in appropriately selected patients, there is an important role for revascularization with either PCI or CABG, with a greater proportion of patients deemed appropriate for PCI compared with CABG.
- Although contemporary studies continue to demonstrate that CABG provides more durable revascularization of LMCA and multivessel coronary disease with lower revascularization rates, this finding is offset by increased morbidity related to cerebrovascular events.

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