

Five-Year Outcomes in Patients With Left Main Disease Treated With Either Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Trial

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Background—Current guidelines recommend coronary artery bypass graft surgery (CABG) when treating significant de novo left main coronary artery (LM) stenosis; however, percutaneous coronary intervention (PCI) has a class IIa indication for unprotected LM disease in selected patients. This analysis compares 5-year clinical outcomes in PCI- and CABG-treated LM patients in the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial, the largest trial in this group to date.

Methods and Results—The SYNTAX trial randomly assigned 1800 patients with LM or 3-vessel disease to receive either PCI (with TAXUS Express paclitaxel-eluting stents) or CABG. The unprotected LM cohort (N=705) was predefined and powered. Major adverse cardiac and cerebrovascular event rates at 5 years was 36.9% in PCI patients and 31.0% in CABG patients (hazard ratio, 1.23 [95% confidence interval, 0.95–1.59]; $P=0.12$). Mortality rate was 12.8% and 14.6% in PCI and CABG patients, respectively (hazard ratio, 0.88 [95% confidence interval, 0.58–1.32]; $P=0.53$). Stroke was significantly increased in the CABG group (PCI 1.5% versus CABG 4.3%; hazard ratio, 0.33 [95% confidence interval, 0.12–0.92]; $P=0.03$) and repeat revascularization in the PCI arm (26.7% versus 15.5%; hazard ratio, 1.82 [95% confidence interval, 1.28–2.57]; $P<0.01$). Major adverse cardiac and cerebrovascular events were similar between arms in patients with low/intermediate SYNTAX scores but significantly increased in PCI patients with high scores (≥ 33).

Conclusions—At 5 years, no difference in overall major adverse cardiac and cerebrovascular events was found between treatment groups. PCI-treated patients had a lower stroke but a higher revascularization rate versus CABG. These results suggest that both treatments are valid options for LM patients. The extent of disease should be accounted for when choosing between surgery and PCI, because patients with high SYNTAX scores seem to benefit more from surgery compared with those in the lower tertiles.

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Key Words: percutaneous coronary intervention ■ stents

The optimal revascularization strategy (coronary artery bypass surgery [CABG] or percutaneous coronary intervention [PCI]) for patients with complex coronary artery disease is a continuing topic of debate. Patients undergoing revascularization of unprotected left main coronary artery (LM) lesions are considered at high risk for adverse cardiovascular

events. Several large studies and meta-analyses have compared outcomes in patients treated with either CABG or PCI with stenting; most have found similar intermediate and long-term safety outcomes (ie, mortality and myocardial infarction

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[MI] and lower stroke rates but an increased need for repeat revascularization with PCI compared with CABG; a few studies have also demonstrated differences in long-term survival with CABG.¹⁻⁷ This analysis evaluated the 5-year outcomes of the predefined LM subgroup of patients who were randomly assigned to receive PCI or CABG in the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial.

Methods

Methods for the SYNTAX trial have been described previously in full⁸⁻¹⁰ and are summarized here. The SYNTAX trial was a prospective, randomized, international, multicenter trial conducted in 17 countries. The study was conducted in accordance with the US Food and Drug Administration Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, the Declaration of Helsinki, the International Conference on Harmonisation, and all local regulations, as appropriate. Institutional review boards at each center approved the study protocol, and all of the patients provided written informed consent.

Subject Selection, Procedure, and Follow-Up

Patients with LM or 3-vessel disease with no previous history of CABG or PCI were assessed a priori using a heart team conference approach, including an interventional cardiologist and a cardiac surgeon, to determine the appropriate method for revascularization (CABG or PCI). If, by consensus, the patient could be offered equivalent revascularization by either technique, the patient was randomly assigned to receive either CABG or PCI with TAXUS Express stents (Boston Scientific, Natick, MA), stratified by LM disease and diabetes mellitus. Patients considered ineligible for 1 technique were entered into 1 of 2 parallel nested registries (the CABG registry for PCI-ineligible patients and the PCI registry for CABG-ineligible patients). The primary end point of the trial was noninferiority of the rate of major adverse cardiac and cerebrovascular events (MACCEs) at 1 year for the PCI arm compared with the CABG arm. All of the patients in the randomly assigned cohort were required to have clinical follow-up yearly through 5 years.⁸⁻¹⁰

Definitions

Definitions of MACCEs and other outcomes have been described previously.^{8,10} In brief, a MACCE was defined as the composite of all-cause death, MI, stroke, and repeat revascularization (via PCI or CABG). Per-protocol symptomatic graft occlusion (GO) and stent thrombosis (ST) were defined as either clinical presentation of an acute coronary syndrome with documentation of a flow-limiting thrombus or occlusion within a bypass graft or adjacent to the anastomosis of a previously bypassed coronary artery (for CABG patients) or within or adjacent to a previously successfully treated artery (for PCI patients) or a Q-wave MI in the territory of ≥ 1 treated vessel within first 30 days. All of the MACCEs and GO and ST events were adjudicated by an independent clinical events committee. Secondary end points included overall MACCE rate and the rates of the individual components of MACCE at 1 month postprocedure and at 6 months and 3 and 5 years postallocation.

Statistical Methods

Initial enrollment was set at 1500 patients but was raised to 1800 to obtain a sufficient number of LM subjects ($n=700$) to detect a difference in 12-month MACCEs between the PCI and CABG arms. However, because of the hierarchical nature of the primary end point analysis, although the subset of LM patients was powered, because the primary end point was not met, the results reported here should be considered hypothesis generating. Procedural and outcomes analyses include all of the lesions in patients with LM disease (with or without additional vessel involvement). Continuous variables were expressed as a mean \pm SD and compared using a 2-sided Student *t* test. Binary variables were expressed as counts and percentages and compared using the χ^2 test. Significance was set at $P<0.05$. Fisher exact test was used in place of the χ^2 test when the total number of samples was ≤ 40 or at least 1 cell count in the contingency table had an expected value <5 . Cumulative event rates were estimated by the Kaplan-Meier method; log-rank test statistics and *P* values were calculated to assess differences between treatment groups for long-term follow-up end points. The Greenwood formula for the SE was used to calculate the 2-sided 95% confidence interval (95% CI)

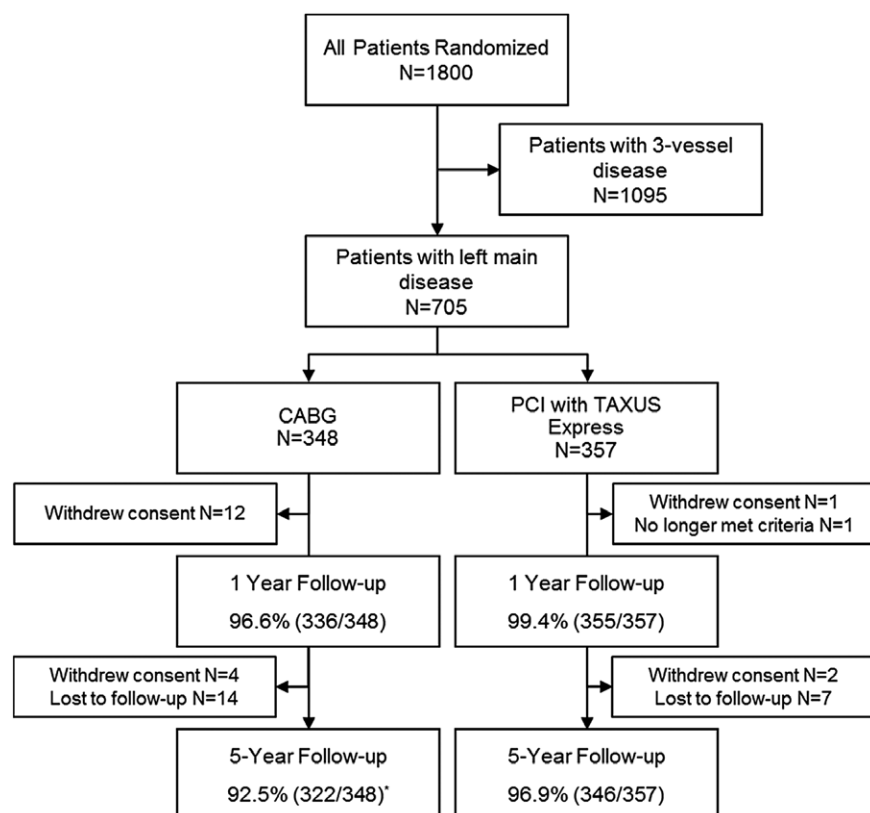


Figure 1. Patient disposition in the prespecified left main coronary artery (LM) subgroup of SYNTAX. *Patients who died within the first year were accounted for at 5-year follow up.

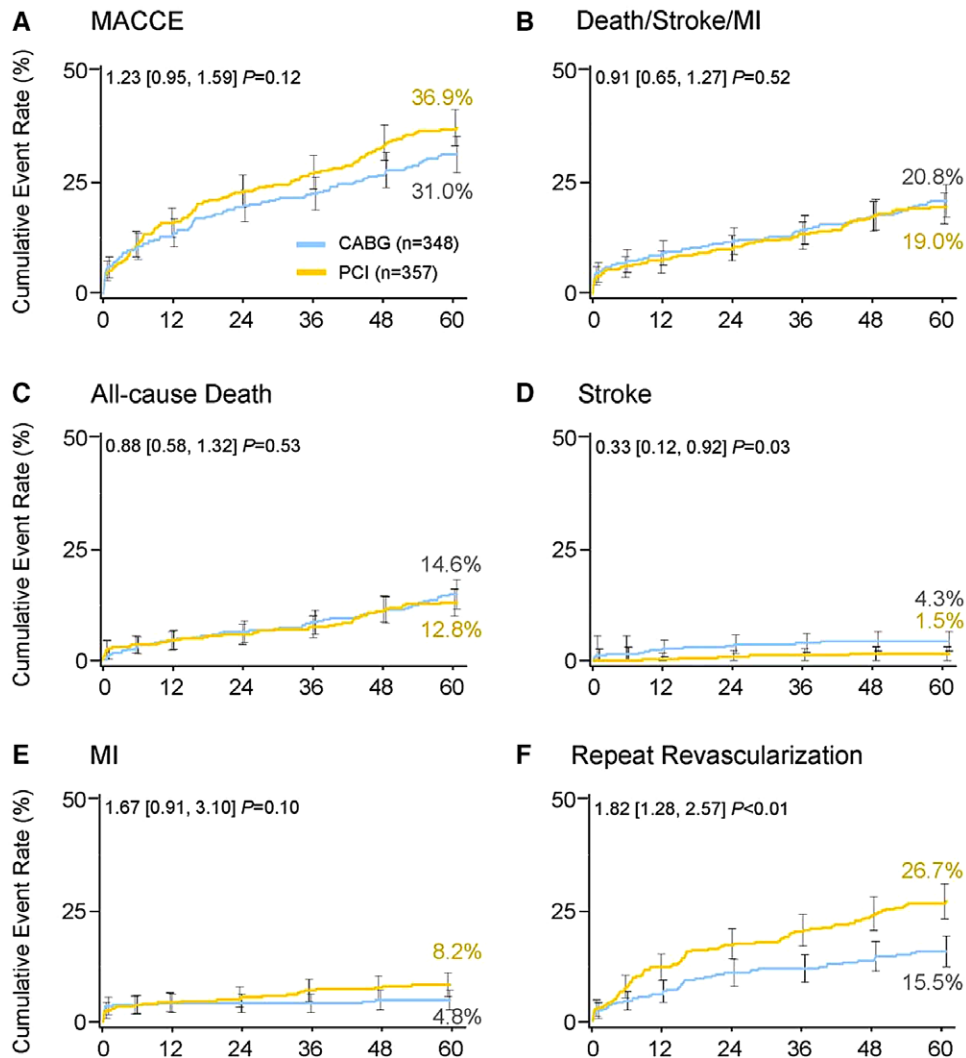


Figure 2. Five-year incidence of cardiac events in left main coronary artery (LM) patients. Hazard ratio and 95% confidence intervals are from the Cox partial likelihood method. Event rates are Kaplan-Meier estimates with a log-rank *P* value.

of the Kaplan-Meier event rates. Hazard ratio (HR) and 95% CIs are from Cox partial likelihood method. Patients were also analyzed post hoc by baseline SYNTAX score tertile (low ≤ 22 , intermediate 23–32, and high ≥ 33) for 5-year MACCE outcomes. Statistical analyses were performed using SAS Software version 9.1 (SAS Institute, Cary, NC).

Results

Patients

A total of 705 patients with LM lesions were enrolled in the randomized arm of SYNTAX (Figure 1). Of these, follow-up data to 5 years are available in 96.9% of patients who underwent PCI with TAXUS Express stents and 92.5% of patients who were randomly assigned to CABG (Figure 1). Baseline patient and lesion characteristics were well balanced between groups and have been published previously along with the 1-year clinical outcomes.¹¹

MACCE Outcomes at 5 Years

MACCE and its components were analyzed in a time-to-event manner over 5 years in the LM cohort. The nonsignificant differences in outcomes in each arm of the trial persisted after

1 year of follow-up. Total MACCE rate at 5 years was 36.9% in patients who received PCI compared with 31.0% in CABG patients (HR, 1.23 [95% CI, 0.95–1.59]; $P=0.12$; Figure 2 and Table 1), which was mainly related to differences in repeat revascularization. The composite safety end point of death/stroke/MI was not significantly different between treatment groups at 5 years postrandomization (PCI 19.0% versus CABG 20.8%; HR, 0.91 [95% CI, 0.65–1.27]; $P=0.57$; Figure 2 and Table 1). All-cause death, cardiac death, and MI rates were not significantly different between groups (all-cause death: PCI 12.8% versus CABG 14.6%; HR, 0.88 [95% CI, 0.58–1.32]; $P=0.53$; cardiac death: PCI 8.6% versus CABG 7.2%; HR, 1.23 [95% CI, 0.71–2.11]; $P=0.46$; MI: PCI 8.2% versus CABG 4.8%; HR, 1.67 [95% CI, 0.91–3.10]; $P=0.10$; Figure 2 and Table 1). In contrast, stroke was significantly increased in CABG-randomized LM patients (PCI 1.5% versus CABG 4.3%; HR, 0.33 [95% CI, 0.12–0.92]; $P=0.03$). Repeat revascularization was significantly increased in PCI-randomized patients (PCI 26.7% versus CABG 15.5%; HR, 1.82 [95% CI, 1.28–2.57]; $P<0.01$; Figure 2 and Table 1). Of the repeat revascularizations, the majority were treated

Table 1. Components of MACCE and Stent Thrombosis Incidence Rates at 5 Years in Left Main Patients

Event	PCI (n=357)	CABG (n=348)	Hazard Ratio PCI vs CABG (95 CI)	P Value
MACCE	36.9 (130)	31.0 (103)	1.23 (0.95-1.59)	0.12
All death/stroke/MI	19.0 (67)	20.8 (69)	0.91 (0.65-1.27)	0.57
All death	12.8 (45)	14.6 (48)	0.88 (0.58-1.32)	0.53
Cardiac death	8.6 (30)	7.2 (23)	1.23 (0.71-2.11)	0.46
Stroke	1.5 (5)	4.3 (14)	0.33 (0.12-0.92)	0.03
MI	8.2 (28)	4.8 (16)	1.67 (0.91-3.10)	0.10
Revascularization	26.7 (90)	15.5 (49)	1.82 (1.28-2.57)	<0.001
PCI	21.6 (73)	13.8 (43)	1.67 (1.15-2.43)	0.007
CABG	7.9 (26)	1.7 (6)	4.16 (1.71-10.10)	<0.001
Stent thrombosis/graft occlusion	5.1 (17)	4.4 (14)	1.15 (0.57-2.33)	0.70

Values are given as Kaplan-Meier event rate % (n) and calculated by time to event analyses with log-rank P values. This shows site-reported data. MACCE and its components are calculated after allocation; stent thrombosis/graft occlusion are calculated after index procedure. Per-protocol stent thrombosis is shown. CABG indicates coronary artery bypass graft surgery; CVA, cerebrovascular event; MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

with repeat PCI, with 21.6% of PCI patients and 13.8% of patients in the CABG arm undergoing additional PCI within 5 years (P<0.01). Repeat revascularization with CABG occurred in 7.9% of PCI patients and 1.7% of CABG patients over 5 years (P<0.001).

Over 5 years, symptomatic GO occurred in 14 LM patients in the CABG arm (4.4%), and symptomatic ST occurred in 17 (5.1%) in the PCI arm (P=0.70). In the CABG arm, 2 patients experienced an acute (≤1 day after index procedure) GO, which led to an MI requiring revascularization. One patient had a subacute (2–30 days) GO that received no intervention. The majority of GOs were either late (31–365 days; n=5) or very late (>366 days; n=6). Of these, 2 GOs led to an MI, 1 was revascularized with PCI, and 1 was not treated. All of the other GOs were revascularized with PCI. In the PCI arm, 17 LM patients experienced a symptomatic ST over 5 years (5.1%). Of these, 7 patients had a subacute ST leading to death in 4 cases, an MI in 1 case, and repeat PCI in 2 cases. Two patients experienced a late ST, and 8 patients experienced a very late ST. One patient died, and 4 had MIs that were revascularized. STs in the remaining 5 patients were treated with repeat CABG (n=3) or PCI (n=2). In 6 patients, the ST was located in the LM leading to death in 2 cases.

The subgroup of LM patients with diabetes mellitus consisted of 67 patients (n=30 CABG; n=37 PCI). Although

clearly underpowered for analysis, similar to the overall cohort, the observed MACCE rate seems comparable between treatment groups, with the only statistical difference being an increased revascularization rate with PCI (Table I in the online-only Data Supplement).

Outcomes Stratified by Baseline SYNTAX Score

Rates of MACCE and its components were similar between LM patients receiving PCI or CABG at 5 years in the lower 2 SYNTAX score tertiles (scores between 0 and 32; Figure 3 and Table 2). There appeared to be a survival advantage in LM patients with scores ≤32 who were treated with PCI (Table 2). In contrast, the likelihood of experiencing a MACCE was increased in PCI patients compared with CABG patients with high SYNTAX scores (≥33; Figure 3 and Table 2). In the group of patients with high SYNTAX scores, MACCE, cardiac death, and revascularization were all significantly increased in patients receiving PCI, whereas stroke and MI occurred at similar rates between treatment arms.

Discussion

The SYNTAX study is the largest randomized comparison of PCI versus CABG for the treatment of patients with LM disease. No significant differences were found between groups for 5-year MACCEs. This confirms and extends the results

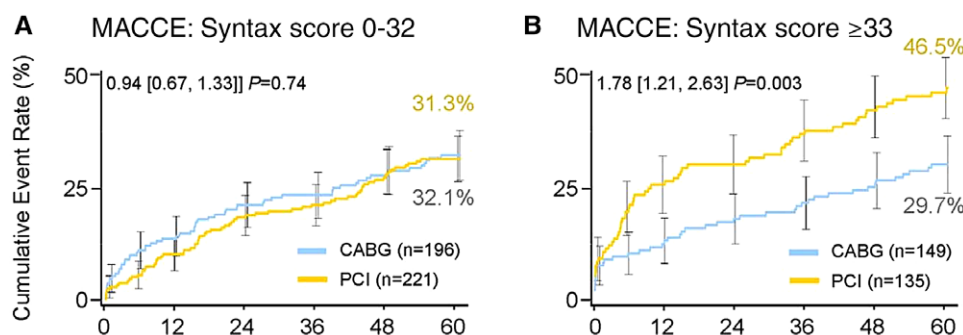


Figure 3. Five-year incidence of cardiac events in patients with (A) low and intermediate (0–32) and (B) high (≥33) Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) scores. Hazard ratio and 95% confidence intervals are from the Cox partial likelihood method. Event rates are Kaplan-Meier estimates with a log-rank P value.

Table 2. Components of MACCE Rates at 5 Years in Left Main Patients Stratified by SYNTAX Score Tertile

Variable	PCI	CABG	Hazard Ratio PCI vs CABG (95% CI)	P Value
SYNTAX score 0–32	n=221	n=196		
MACCE	31.3 (68)	32.1 (60)	0.94 (0.67-1.33)	0.74
All death/stroke/MI	14.8 (32)	19.8 (37)	0.71 (0.44-1.14)	0.16
All death	7.9 (17)	15.1 (28)	0.50 (0.27-0.91)	0.02
Cardiac death	4.2 (9)	8.3 (15)	0.50 (0.22-1.14)	0.09
Stroke	1.4 (3)	3.9 (7)	0.35 (0.09-1.35)	0.11
MI	6.1 (13)	3.8 (7)	1.58 (0.63-3.95)	0.33
Revascularization	22.6 (48)	18.6 (33)	1.23 (0.79-1.91)	0.36
PCI	19.3 (41)	17.1 (30)	1.15 (0.72-1.83)	0.57
CABG	6.2 (13)	1.5 (3)	3.68 (1.05-12.91)	0.03
SYNTAX score ≥33	N=135	N=149		
MACCE	46.5 (62)	29.7 (43)	1.78 (1.21-2.63)	0.003
All death/stroke/MI	26.1 (35)	22.1 (32)	1.23 (0.76-1.98)	0.40
All death	20.9 (28)	14.1 (20)	1.59 (0.90-2.83)	0.11
Cardiac death	15.8 (21)	5.9 (8)	2.98 (1.32-6.73)	0.006
Stroke	1.6 (2)	4.9 (7)	0.32 (0.07-1.54)	0.13
MI	11.7 (15)	6.1 (9)	1.88 (0.82-4.30)	0.13
Revascularization	34.1 (42)	11.6 (16)	3.30 (1.86-5.88)	<0.001
PCI	25.6 (32)	9.5 (13)	3.07 (1.61-5.85)	<0.001
CABG	11.2 (13)	2.0 (3)	5.01 (1.43-17.57)	0.005

Values are given as Kaplan-Meier event rate % (n) and calculated by time to event analyses with log-rank *P* values. This is site-reported data. MACCE and its components are calculated after allocation. CABG indicates coronary artery bypass graft surgery; CVA, cerebrovascular event; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

observed at 1 year, which also showed no significant differences in MACCEs in this LM subgroup of patients, in contrast with the global cohort where the results were clearly in favor of surgery.¹¹ In addition, outcomes in patients with LM coronary artery disease have been shown to be related to the severity (or complexity) of the downstream disease, rather than the actual presence of LM coronary artery disease,¹² which the present analysis corroborates.

Although overall MACCEs in the LM subgroups were pre-specified and powered, the SYNTAX trial used a hierarchical statistical testing plan whereby testing of the LM subgroup would occur only if the primary end point was met. The non-inferiority end point of 12-month MACCEs was not met in the overall population; thus, the analysis of LM patients presented here should be considered observational and hypothesis generating.^{10,13} However, consistent with other randomized trials and nonrandomized registries of LM patients, mortality was similar in both treatment groups at 5 years.^{1,3,14–19} Only 1 propensity matched registry found increased mortality in LM patients treated with drug-eluting stents compared with CABG.²

Procedure-related stroke is a serious and well-known complication after CABG.²⁰ Stroke was significantly increased in LM CABG-randomized patients at 1 year and remains significantly increased at 5 years. The majority of strokes in the CABG arm occurred acutely (<30 days), whereas most occurred >30 days after the index procedure in the PCI arm. The cumulative stroke curves for LM patients remain parallel

after 1 year. This is different from the observed stroke rate in the global SYNTAX population (LM plus 3-vessel disease), where the stroke rate was significantly increased with CABG at 1 year and no more significant at 5 years.²¹

Significant increases in repeat revascularization were observed within 1 year after the index procedure.^{10,11} The rate of repeat revascularization in the LM PCI subgroup at 5 years (26.7%) is consistent with other published randomized trials and registries comparing PCI- and CABG-treated LM patients (15.7–28.4%^{2,3,14–19}) but was higher in the CABG LM cohort (15.5%) compared with these studies (3.2–8.4%).^{2,3,14–19} In the patient population analyzed, the increased likelihood of repeat revascularization with PCI is a tradeoff; CABG has an increased stroke rate.^{2–7,11} This difference in outcome between the 2 revascularization strategies is important to highlight in patient discussions, because the relative importance attributed to each varies.

Revascularization was also increased in LM patients with medically treated diabetes mellitus who were randomly assigned to PCI compared with CABG; all of the other events including the composite MACCE seem to be comparable. This must be treated with caution because of the small number of patients (67 patients). Excess mortality has been observed in other studies of diabetic patients with complex coronary disease but not in the SYNTAX trial.^{2,22,23}

At 5 years, the MACCE rate in PCI LM patients with low or moderate disease complexity (low and intermediate SYNTAX

scores) was similar to patients randomly assigned to CABG. However, in patients with high SYNTAX scores (≥ 33), the MACCE rate was significantly increased in the PCI arm. Increased coronary disease did not impact stroke rate in either arm, similar to the findings from a large meta-analysis of acute (30 days) and midterm (1 year) stroke between CABG and PCI.²⁰ Updated LM revascularization guidelines have recently assigned a class IIb recommendation to PCI in patients with low/intermediate SYNTAX scores (or a class IIa indication in selected patients without coexisting multivessel disease).^{24,25} Because the SYNTAX trial was designed in 2004, new generations of stents have emerged and proven superior to the TAXUS Express stent. In addition, adjunct medication and techniques have improved significantly and together with the evolution of the stent design have reduced mortality. Surgical techniques have evolved as well. The ongoing Evaluation of Xience Prime or Xience V Versus CABG for Effectiveness of Left Main Revascularization (EXCEL) trial is enrolling LM patients with mild-to-moderate anatomic complexity (SYNTAX score ≤ 32) using a more contemporary stent and current surgical techniques and will shed more light on the issues of LM revascularization; EXCEL will compare the 3-year primary composite end point of death, MI, and stroke in patients treated with PCI with drug-eluting stents with CABG.

Potentially, with a heart team available, triaging of patients to PCI or CABG will provide optimal outcomes for the patient. SYNTAX has been credited as the trial that formalized the heart team concept, a multidisciplinary group of healthcare professionals who assess and manage patients with complex coronary artery disease.^{26,27} Recent updates to the 2010 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery Guidelines for Coronary Revascularization²⁵ and the 2011 American College of Cardiology Guidelines for PCI and CABG^{28,29} list the heart team as a class 1 indication for treatment of coronary artery disease. A team-based approach to patient care, especially in patients with complex disease or circumstances, will likely further improve outcomes.

Study Limitations

Hierarchical primary end point testing of the SYNTAX study allowed testing of the LM subgroup only if the overall comparison reached statistical significance. Because noninferiority of the primary end point was not met, the results from this analysis must be considered hypothesis generating only and should be interpreted with care. The results may have been confounded by the heterogeneity of the LM subgroup, which consisted of LM patients with 0-, 1-, 2-, or 3-vessel disease. Although the SYNTAX study was designed to follow patients for 5 years, additional differences between the treatment arms may develop over time.

Conclusions

The SYNTAX trial is currently the largest randomized, controlled trial comparing PCI with CABG in complex coronary disease with a prespecified and powered LM subgroup. CABG has been the gold standard for revascularization of the LM vessel; however, this hypothesis-generating subanalysis of the SYNTAX trial suggests that PCI can provide equivalent long-term (to 5 years) death/stroke or MI to CABG, in particular in the subset of LM subjects with SYNTAX scores < 33 .

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Disclosures

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CLINICAL PERSPECTIVE

Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) is a landmark trial with the goal of assessing the optimal revascularization strategy for patients with de novo 3-vessel or unprotected left main (LM) disease. We present here the 5-year results of the LM subgroup. In view of the 1-year outcome achieved in this subgroup, percutaneous coronary intervention (PCI) has been given, in the current guidelines, a Class IIa indication for unprotected LM disease in selected patients without additional multivessel disease. This analysis aims to add additional data to support these recommendations. The SYNTAX study is remarkable for a number of reasons including its all-comers design, limited exclusion criteria, use of a Heart Team, and development of the SYNTAX score. There were 705 patients in the LM subgroup, making this the largest powered, randomized comparison of revascularization treatment for LM disease. After a 5-year follow-up in the LM cohort, no difference in overall major adverse cardiac and cerebrovascular events was found between treatment groups. Stroke was significantly increased in the coronary artery bypass graft surgery LM group and repeat revascularization was significantly increased in the PCI LM arm at 5 years. These results suggest that revascularization with PCI has comparable safety and efficacy outcomes to coronary artery bypass graft surgery for patients with LM disease. Major adverse cardiac and cerebrovascular events were similar, if not better for PCI, between PCI and coronary artery bypass graft surgery in patients with low or intermediate SYNTAX scores but significantly increased in PCI patients with high scores (≥ 33). This suggests that PCI can be a viable alternative to surgery in the treatment of patients with LM disease of mild or moderate extent and severity (higher tercile of the SYNTAX score).

Five-Year Outcomes in Patients With Left Main Disease Treated With Either Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Trial

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Supplementary Table 1. Components of MACCE and Stent Thrombosis Incidence Rates at 5 Years in Left Main Patients with and without Diabetes

Event	DM		N-DM	
	PCI	CABG	PCI	CABG
	(N=75)	(N=75)	(N=271)	(N=247)
Post-Allocation				
MACCE	49.3% (37/75)	40.0% (30/75)	34.3% (93/271)	30.0% (74/247)
All Death/Stroke/MI	22.7% (17/75)	30.7% (23/75)	18.5% (50/271)	19.0% (47/247)
All Death	18.7% (14/75)	18.7% (14/75)	11.4% (31/271)	14.2% (35/247)
Stroke	1.3% (1/75)	6.7% (5/75)	1.5% (4/271)	3.6% (9/247)
MI	8.0% (6/75)	9.3% (7/75)	8.1% (22/271)	3.6% (9/247)
Revascularization	37.3% (28/75)	17.3% (13/75)	22.9% (62/271)	14.6% (36/247)
PCI	30.7% (23/75)	13.3% (10/75)	18.5% (50/271)	13.4% (33/247)
CABG	8.0% (6/75)	4.0% (3/75)	7.4% (20/271)	1.2% (3/247)
Post-Procedure Stent				
Thrombosis/Graft	6.7% (5/75)	6.7% (5/75)	4.4% (12/271)	3.6% (9/247)
Occlusion				

Values are given as % (n/N) and calculated binary analysis.