8-1-2022

Revascularization Strategies for Stable Left Main Coronary Artery Disease: Analysis of Current Evidence

Shashank Shekhar

Divyanshu Mohananey

Pedro Villablanca

Sudhi Tyagi

Juan A. Crestanello

See next page for additional authors

Authors

Shashank Shekhar, Divyanshu Mohananey, Pedro Villablanca, Sudhi Tyagi, Juan A. Crestanello, Iván J. Núñez Gil, and Harish Ramakrishna

Journal of Cardiothoracic and Vascular Anesthesia 36 (2022) 3370–3378

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Expert Review

Revascularization Strategies for Stable Left Main Coronary Artery Disease: Analysis of Current Evidence

Shashank Shekhar, MD[*], Divyanshu Mohananey, MD[†], Pedro Villablanca, MD[‡], Sudhi Tyagi, MD[†], Juan A. Crestanello, MD[§], Iván J. Núñez Gil, MD, PhD, FESC[||], Harish Ramakrishna, MD, FACC, FESC, FASE[¶,1]

[*]*Department of Cardiovascular Medicine, Heart, and Vascular Institute, Cleveland Clinic, Cleveland, OH*
[†]*Department of Cardiovascular Medicine, Medical College of Wisconsin, Milwaukee, WI*
[‡]*Interventional Cardiology, Henry Ford Hospital, Detroit, MI*
[§]*Division of Cardiovascular Surgery, Mayo Clinic, Rochester, MN*
[||]*Interventional Cardiology Consultant, Cardiovascular Institute, Hospital Clínico San Carlos, Madrid, Spain*
[¶]*Division of Cardiovascular and Thoracic Anesthesiology, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN*

Key Words: left main coronary artery disease; clinical trials; percutaneous coronary intervention; coronary artery bypass grafting; ischemic heart disease; LMCAD

ISCHEMIC HEART disease (IHD), also referred to as coronary artery disease (CAD) and atherosclerotic cardiovascular disease, is the most prevalent cardiovascular illness in the western world and is responsible for significant morbidity and mortality.[1-3] Recently published data from the Global Burden of Diseases estimated that around 1.72% of the world's population (126 million individuals) were affected by IHD[3] and that IHD was the leading cause of death in 9 million people globally in 2017. In the United States, the prevalence of IHD is 2,929 per 100,000 individuals, and the World Heart Federation estimates the cost per episode of IHD to be upward of $5,000.[3]

Due to the large territory at risk for myocardial ischemia, left main coronary artery disease (LMCAD) presents with significant life-shortening morbidity and mortality.[4] Traditionally, revascularization with coronary artery bypass grafting (CABG) was the treatment of choice for patients with LMCAD and triple-vessel disease. However, significant advances in the techniques and stents of percutaneous coronary intervention (PCI) have made it a viable contender for revascularization in patients based on their anatomic complexity. As such, several trials, meta-analyses, single-center, and observational studies recently have been published to evaluate the outcomes of LMCAD patients undergoing PCI and/or CABG.

The authors here summarize and critically appraise key clinical trials and other studies in the treatment of LMCAD.

Medical Management of LMCAD

The last few decades have seen a variety of newer-age disease-modifying drugs (such as statins, inhibitors of the renin-angiotensin-aldosterone system, and antiplatelet agents, such as P2Y12 inhibitors) that are effective in reducing adverse cardiovascular events in patients with CAD.[5-11] However, most of the randomized clinical trials (RCTs) that previously defined the guidelines for the treatment of patients with LMCAD were conducted in an era when medical therapy largely was limited, and, as such, only a fraction of patients

[1]*Address correspondence to* Harish Ramakrishna, MD, FACC, FESC, FASE; Division of Cardiovascular and Thoracic Anesthesiology, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55901.
E-mail address: Ramakrishna.harish@mayo.edu (H. Ramakrishna).

https://doi.org/10.1053/j.jvca.2021.12.016

with "medically managed" LMCAD were put on drugs such as beta-blockers and aspirin.[12-14] Despite the dearth of evidence-based optimal medical therapy, the aforementioned RCTs found favorable outcomes in lower-risk patients with LMCAD (with <70% stenosis or with preserved left ventricular function) who were medically managed alone (66% survival at 3-years). As such, lifestyle interventions and guideline-directed secondary preventions should be encouraged in patients with LMCAD, similar to how these are implemented in patients with non-left main disease. There are, however, unmet clinical challenges, such as differentiating between significant and nonsignificant left main disease from angiographic and clinical characteristics, that often make even the most experienced physicians wary of deferring revascularization in favor of medical therapy. With the advent of newer invasive techniques, such as intravascular ultrasound (IVUS) and fractional flow reserve (FFR), cardiologists may be able to better tailor the treatment aspects of patients with revascularization in conjunction with optimal medical therapy.

Evaluation of LMCAD

Although patients with significant LMCA stenosis usually are symptomatic, it is not uncommon for significant LMCAD to be found incidentally in stable patients undergoing coronary angiography.[14] While there is significant interobserver variability in visually assessing intermediate LM stenoses (30%-70%), the angiographic assessment of LM stenosis ≥70% is fairly accurate and reproducible.[15,16] In order to mitigate the unwarranted risks from premature CABG in noncritical lesions, it is imperative to use noninvasive and/or invasive modalities to evaluate LMCA stenosis in conjunction with angiography.[16,17] From a noninvasive standpoint, certain features are highly indicative of significant LM or equivalent disease, including (1) Duke treadmill score ≤11, (2) stress-induced sustained ventricular tachyarrhythmia or nonsustained ventricular tachyarrhythmia >30 seconds or ST-segment elevation, (3) exercise left ventricular ejection fraction (LVEF) ≤35%, (4) large reversible anterior perfusion defect (≥10% left ventricular involvement on nuclear perfusion or ≥12.5% left ventricular involvement on cardiac magnetic resonance imaging) or multiple reversible perfusion defects of moderate size, (5) stress-induced left ventricular dilation or increased lung uptake in the setting of moderate perfusion defect or large fixed perfusion defect, (6) echocardiographic wall motion abnormality involving >2 segments developing at low-dose dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min).[18] Invasively, while tools like IVUS help in describing the anatomic extent of the LM lesion, the hemodynamic significance of a clinically unclear LM stenosis lesion is best evaluated by pressure wire assessment of FFR. Intracoronary imaging with IVUS is helpful in describing the anatomic extent of the disease, determination of plaque extent, as well as in determining ostial involvement of daughter branches. In patients with distal lesions and those treated with a 2-stent strategy, IVUS also helps in ensuring the optimum expansion and apposition of stents after LM PCI. IVUS, thus, is helpful in estimating the overall ischemic burden of the LM lesion. as well as in improving the clinical outcomes of patients.[19,20] However, the cut-off for the minimal luminal area for left main lesions varies in different populations, and, as such, the values ascribed to IVUS should be interpreted with caution. The hemodynamic significance of an LM stenosis lesion is best assessed by FFR. Studies have shown favorable long-term outcomes with deferring revascularization in patients with angiographically intermediate LM lesions with an FFR of ≥0.80.[16] An LM lesion is assumed to be hemodynamically significant or insignificant if the FFR of the lesion is >0.85 or ≤0.80, respectively.[21] However, for lesions with an FFR between 0.81 and 0.84, the hemodynamic significance of the lesion cannot be accurately determined, and as such, imaging with IVUS is preferred in these cases.[19,20] With all the tools that are available, both IVUS and FFR complement the angiographic findings in the evaluation of an LM lesion.[22]

Current Guidelines

The current guidelines base the method of revascularization in patients with LMCAD on the anatomic complexity of the coronary artery disease (SYNTAX score) and the surgical risk of the patients.[4] The recommendations come largely on the basis of the results of the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial[23-25] and smaller underpowered studies.[23-26] In the United States, the existing American College of Cardiology (ACC)/American Heart Association (AHA) clinical guidelines continue to champion CABG as a Class I indication for myocardial revascularization in patients with LMCAD with coexisting complex multivessel disease (SYNTAX score ≥33).[27] PCI, on the other hand, has a Class IIa recommendation in patients with increased surgical bypass risk with isolated LM stenosis involving the ostium or shaft and without coexisting multivessel disease. For patients with LM stenosis involving the distal bifurcation or with a low or intermediate SYNTAX score (≤32) and at an elevated surgical risk, PCI has a Class IIb indication ("may be reasonable"). The current European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines have a Class I recommendation for PCI in patients with low anatomic complexity, a Class IIa recommendation for patients with intermediate anatomic complexity, and a Class III recommendation for patients with high anatomic complexity (Table 1).[28]

Review of RCTs

SYNTAX Trial

The first results that largely defined the recommendation of CABG for left main CAD based on SYNTAX scores came from the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial.[23-25] This trial formed the core of all major cardiology and cardiothoracic surgery societal guideline recommendations.

Table 1
Guidelines for the Type of Revascularization in Patients With Left Main Coronary Artery Disease

Class*	(Level†)	Recommendation	
ACC/AHA Guidelines (2011)[27]			
I	B	CABG recommended to improve survival in patients with ≥50% diameter stenosis of left main coronary artery	
IIa	B	PCI is a reasonable alternative to CABG to improve survival in patients with ≥50% diameter stenosis of left main coronary artery with: • Low SYNTAX score ≤22 (ostial or trunk LMCAD) and • STS surgical risk score ≥5%	
IIa	B	PCI is reasonable to improve survival in patients with UA/NSTEMI when an unprotected left main coronary artery is the culprit lesion and the patient is not a candidate for CABG	
IIa	C	PCI to improve survival is reasonable in patients with acute STEMI when an unprotected left main coronary artery is the culprit lesion, distal coronary flow is less than TIMI grade 3, and PCI can be performed more rapidly and safely than CABG	
IIb	B	PCI may be reasonable to improve survival in patients with ≥50% diameter stenosis of left main coronary artery with: • Low-intermediate SYNTAX score <33 (bifurcation LMCAD), and • STS surgical risk score >2%,	
III	B	PCI to improve survival should not be performed in stable patients with ≥50% diameter stenosis of left main coronary artery with unfavorable anatomy for PCI and who are good candidates for CABG	
ESC/EACTS Guidelines[28]			
I	A	For CABG	
I	A	For PCI	LMCAD with Low SYNTAX score (0-22)
I	A	For CABG	
IIa	A	For PCI	LMCAD with Intermediate SYNTAX score (23-32)
I	A	For CABG	
III	B	For PCI	LMCAD with High SYNTAX score (≥33)‡

NOTE. SYNTAX score calculation information is available at http://www.syntaxscore.com
Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ESC/EACTS, European Society of Cardiology/European Association for Cardio-Thoracic Surgery; LMCAD, left main coronary artery disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; STS risk score, Society of Thoracic Surgeons-predicted risk of operative mortality; STEMI, ST-elevation myocardial infarction; SYNTAX, Synergy between Percutaneous Coronary intervention with TAXUX and Cardiac surgery; TIMI, thrombolysis in myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction.
* Class of recommendation.
† Level of evidence.
‡ PCI should be considered if Heart Team is concerned about the surgical risk or if the patient refuses CABG after adequate counselling by the Heart Team.

The SYNTAX trial was a prospective, multinational trial conducted in 85 centers across the United States and Europe between 2005 and 2007, in which 1,800 patients with de novo left main or 3-vessel disease were randomly assigned to undergo CABG or PCI with first-generation paclitaxel-eluting stents. Patients were grouped not only based on the number of stenotic vessels, but also on their SYNTAX scores. Patients undergoing PCI were prescribed antiplatelet medications as per directions for the use of the Taxus Express stent and local clinical practice. All patients who underwent randomization were indefinitely prescribed aspirin.

The primary endpoint of the trial was a composite of major cardiovascular or cerebrovascular events (MACCE), including all-cause mortality, stroke, myocardial infarction (MI), and the need for repeat revascularization at 12 months after randomization. At 1 year, patients undergoing CABG and PCI had similar rates of MACCE (13.7% *v* 15.8% respectively; p = 0.44). While the rate of repeat revascularization was significantly higher in patients who underwent PCI (11.8% *v* 6.5% for CABG; p = 0.02), the stroke rate was higher in the CABG group (2.7% *v* 0.3% for PCI; p = 0.01).

For patients with LMCAD, the results from the 5-year analysis of this trial not only confirmed the results at 1 year but also demonstrated significant advantage of CABG in the hard components of the composite endpoint; namely, death, stroke, and MI in patients with LM.[25] In patients with LMCAD, while the MACCE rate was numerically higher in patients who received PCI as compared to CABG, it did not meet statistical significance (36.9% *v* 31%; hazard ratio [HR] 1.23 [95% confidence interval (CI), 0.95-1.59]; p = 0.12). Additionally, the composite safety endpoint of death/stroke/MI was not significantly different between the 2 treatment strategies (PCI *v* CABG, 19% *v* 20.8%; HR 0.91 [95% CI, 0.65-1.27]; p = 0.57). Further, stroke rates were significantly higher in patients in the CABG group (4.3% *v* 1.5% for PCI; HR 0.33 [95% CI 0.12-0.92]; p = 0.03), while the rate of repeat revascularization was greater in patients randomized to the PCI group (26.7% *v* 15.5% for CABG; HR 1.82 [95% CI, 1.28-2.57]; p < 0.01). When stratified by the baseline SYNTAX scores, patients with a higher SYNTAX score (≥33) undergoing CABG had lower incidences of MACCE (29.7% *v* 46.5% for PCI; HR 1.78 [95% CI 1.21-2.63]; p = 0.003), cardiac death (5.9% *v* 15.8% for PCI; HR 2.98; [95% CI, 1.32-6.73]; p = 0.006), revascularization (11.6% *v* 34.1% for PCI; HR 3.30 [95% CI 1.86-5.88; p < 0.001), and MI (6.1% *v* 11.7% for PCI; HR 1.88 [95% CI 0.82-4.30]; p = 0.13). On the other hand, patients undergoing CABG had a higher incidence of stroke (4.9% *v* 1.6% for PCI; HR 0.32 [95% CI 0.07-1.54]; p = 0.13). The 10-year follow-up results of this trial recently were published by the SYNTAX Extended Survival study

investigators based on data from 1,689 (94%) patients, out of whom 705 had LMCAD.[29,30] At 10 years, there was no significant difference in all cause deaths between patients with LMCAD undergoing PCI versus CABG (27% *v* 28%, respectively; HR 0.92, [95% CI 0.69-1.22]).

A major limitation of this trial was that it was powered toward patients with intermediate and high SYNTAX scores. Additionally, PCI was performed with first-generation paclitaxel-eluting stents; newer generation drug-eluting stents (DES) have been shown to be associated with significantly improved outcomes.[31,32]

LE MANS Trial

The 10-year outcomes of the Left Main Coronary Artery Stenting (LE MANS) trials were published in 2016.[33] The LE MANS trial was the first prospective study to evaluate left main stenting and CABG for unprotected LM stenosis with low and medium complexity of coexisting CAD according to SYNTAX score. The trial enrolled 105 symptomatic patients with documented myocardial ischemia, with at least 50% stenosis of the unprotected LM coronary artery. Exclusion criteria were patients with acute MI, total occlusion of the LM, comorbid conditions, or coronary anatomic considerations that increased the surgical risk to a EuroSCORE of 8 or more, stroke (or transient ischemic attack) within 3 months, renal dysfunction, or contraindication to antiplatelet therapy.[34] Patients were randomized to receive either PCI or CABG. For patients undergoing PCI, medical therapy with aspirin and a thienopyridine (clopidogrel or ticlopidine) was started at least 2 days before the procedure, with unfractionated heparin being given in standard doses. Intravenous glycoprotein IIb/IIIa blockers were used in patients with complex coronary lesions and unstable angina. All patients undergoing surgical revascularization were prescribed antiplatelet therapy for at least 12 months after the procedure. The primary endpoint of the LE MANS trial was LVEF assessed by 2-dimensional echocardiography at 1 year. At 10 years, there was a trend toward higher LVEF with PCI compared to CABG 54.9 ± 8.3% *v* 49.8 ± 10.3%; p = 0.07). Although not statistically significant, the incidence of MACCE was lower in the PCI group in comparison to the CABG group (52.2% *v* 62.5%; p = 0.42). There was a trend toward higher very long-term MACCE-free survival in the PCI group (HR: 1.57; 95% CI: 0.90-2.73; p = 0.10). The results were similar in favoring PCI over CABG with regard to the incidence of MI, long-term MI survival, and stroke and/or transient ischemic attack, with the analysis not reaching statistical significance. Of note, the need for repeated revascularizations was similar between both groups (HR: 1.34; 95% CI: 0.61-2.95; p = 0.46).

The study showed equipoise between LM stenting and CABG. However, this study was underpowered to provide conclusive answers,[26] and the authors concluded that PCI provided numerically, but statistically nonsignificant, favorable long-term outcomes up to 10 years over CABG in patients with unprotected LM coronary artery stenosis with low and medium complexity of coexisting CAD. It is also important to note that only 35% of stents implanted in the trial were DES, whereas >80% of patients received arterial bypass grafts. This created a difference in the quality of revascularization, and the data are not representative of contemporary PCI strategy with new-generation DES.

PRECOMBAT

The Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial was a noninferiority trial in which 600 patients with unprotected left main coronary artery disease were randomized to undergo PCI with a sirolimus-eluting stent or CABG, in Korea, from April 2004 to August 2009.[30,35]

Patients with a left main coronary artery stenosis of >50% (estimated visually) and with a diagnosis of stable angina, unstable angina, silent ischemia, or non-ST-segment elevation MI, were included in this study. All patients undergoing PCI were prescribed aspirin plus clopidogrel (loading dose, 300 mg) or ticlopidine (loading dose, 500 mg) before or during the procedure. Postprocedurally, patients were prescribed 100 mg/d aspirin indefinitely, and 75 mg/d clopidogrel, or 250 mg/d ticlopidine for at least 6 months. The primary endpoint was the incidence of MACCE (composite of death from any cause, MI, stroke, or ischemia-driven target-vessel revascularization). The mean age of the enrolled patients was 62.3 ± 9.7 years, with 76% being males. The mean SYNTAX score was 24.8 ± 10.3 (low in 42.4%, intermediate in 35.3%, and high in 22.3%). The trial showed no significant difference between the 2 treatment groups in the incidences of MACCE and mortality at 2 and 5 years.[35,36] At 5 years, there was no difference between the 2 groups for mortality (5.7% *v* 7.9% for CABG; HR, 0.73 [95% CI 0.39-1.37], p = 0.32), MACCE (17.5% *v* 14.3% for CABG; HR, 1.27 [95% CI 0.84-1.90], p = 0.26), MI (2% *v* 1.7% for CABG; HR, 1.20 [95% CI 0.37-3.93], p = 0.76), stroke (0.7% *v* 0.7% for CABG; HR, 0.99 [95% CI 0.14-7.02] p = 0.99). However, there was a significantly increased rate of repeat revascularization in patients undergoing PCI (13% *v* 7.3% for CABG; HR, 1.86 [95% CI 1.09-3.17], p = 0.020). In patients with CAD involving isolated LM stenosis, the incidence of MACCE for patients undergoing CABG was greater, albeit statistically insignificant, than PCI (14.8% *v* 7.4%, HR, 0.48 [95% CI 0.09-2.47]; p = 0.37).

Out of 600 patients, 10-year follow-up was achieved in 288 (96%) patients randomized to PCI and 288 patients (96%) randomized to CABG, respectively.[37] The primary outcomes of MACCE events between PCI and CABG groups were 29.8% *v* 24.7% (HR with PCI *v* CABG, 1.25 [95% CI, 0.93-1.69]). There were no significant differences in the secondary composite outcomes of death, MI, or stroke (18.2% *v* 17.5%; HR 1.00 [95% CI, 0.70-1.44]) and all-cause mortality (14.5% *v* 13.8%; HR 1.13 [95% CI, 0.75-1.70]) between the PCI and CABG groups. Furthermore, the 10-year incidences of ischemia-driven target-vessel revascularization (16.1% *v* 8.0%; HR 1.98 [1.21-3.21]) and any revascularization (21.3% *v* 10.6%; HR 2.04 [1.33-3.11]) were higher after PCI than after CABG.

PCI patients with a high SYNTAX score had a higher rate of ischemia-driven revascularization. In patients with isolated involvement of the LM vessel, the incidence of MACCE in PCI versus CABG was 15.1% *v* 14.9% (HR, 1.55 [95% CI 0.40-5.95]. The authors thus concluded that there was no significant difference in the primary outcome of MACCE between PCI and CABG in patients with LMCA disease. However, due to a wide non-inferiority margin and a relatively small sample size, the study had insufficient statistical power to allow for a firm conclusion, and the results should, at best, be considered hypothesis-generating.[4,38]

EXCEL Trial

One of the more exciting yet controversial debates in cardiology in recent times has been about the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial.[39] The prospective, open-label, noninferiority study, which was conducted at 126 centers in 17 countries around the world, included 1,905 patients with stable or unstable angina with an LM stenosis of 70% assessed visually, or 50%-to-70% determined by invasive or non-invasive methods, and a SYNTAX score of ≤32. Some of the key exclusion criteria were: (1) PCI of the left main trunk at any time prior to randomization, or non-left main trunk within 1 year of randomization; (2) prior CABG; (3) need for any concomitant cardiac surgery; (4) inability to tolerate dual-antiplatelet therapy for 1 year; (5) SYNTAX score ≥33; and (6) visually estimated LM reference vessel diameter <2.25 mm or >4.25 mm.

Patients were randomized to PCI with Xience everolimus-eluting stents (n = 948) or CABG (n = 957). PCI was performed with a goal of achieving complete revascularization of all ischemic territories, with dual-antiplatelet therapy initiated before the procedure and continued for a minimum of 1 year thereafter. The use of intravascular ultrasonographic guidance was strongly encouraged. While the use of heparin or bivalirudin was allowed for procedural anticoagulation, glycoprotein IIb/IIIa inhibitors were discouraged. CABG, performed with or without cardiopulmonary bypass, was done with the recommended use of epiaortic ultrasonography and transesophageal ultrasonography, with aspirin being administered during the perioperative period and clopidogrel (in accordance with the local standard of care) during the follow-up period. The mean age of patients was 66 years. The long-term results of the trial recently were published.[40] The trial displayed an interesting temporal relationship of comparative outcomes. In the early postprocedural phase (at 30 days), the primary composite endpoint of death, stroke, or MI occurred less frequently in the PCI group in comparison to the CABG group (4.9% *v* 7.9%; HR 0.61 [95% CI 0.42-0.88]; p = 0.008). Patients undergoing PCI also had better outcomes in the individual components of stroke (0.6% *v* 1.3% for CABG; HR, 0.50 [95% CI 0.19-1.32]), MI (3.9% *v* 6.3% for CABG; HR, 0.63 [95% CI 0.42-0.94], and ischemia-driven revascularization (0.6% *v* 1.4% for CABG; HR, 0.46 [95% CI 0.17-1.21]. This likely represented the invasiveness of cardiac surgery as compared to PCI. However, this differential risk was attenuated between 30 days and 12 months of follow-up, with the primary composite outcome occurring in 4.1% of PCI patients *v* 3.8% of CABG patients (HR, 1.07 [95% CI 0.68-1.70]). PCI patients had a lower stroke rate (0.5% *v* 0.8% for CABG; HR 0.71 [95% CI 0.22-2.23]) but a higher event rate for MI (1.7% *v* 1.1% for CABG; HR 1.58 [95% CI 0.72-3.48]) and ischemia-driven revascularization (6.4% *v* 3.1% for CABG; HR 2.10 [95% CI 1.34-3.30]) during this period. Thereafter, the curves again were seen to diverge as the authors approached 5-year follow-up. At 5 years, the primary outcome was 22.0% *v* 19.2% in PCI *v* CABG arms (95% CI 0.95-1.50; p = 0.13). This also can be seen in the NOBLE trial, in which, at 1 year, there were more deaths in the surgical arm than the PCI (17 with CABG *v* 9 with PCI). The longer-term results, however, showed a catch-up phenomenon, with 54 deaths in the PCI group and 50 in the CABG group. Analyzing the individual results of the EXCEL trial, there was noted to be significantly higher all-cause mortality in the PCI arm (9.9% *v* 13.0% with PCI; odds ratio [OR] 1.38, 95% CI 1.03-1.85). However, 18 of 30 excess deaths in the PCI group were adjudicated as noncardiovascular deaths, and only 5 were cardiovascular deaths, with the rest being of unknown cause. These results were in line with the NOBLE trial, in which the risk of death at 5 years was similar in the PCI and CABG arm. Of note, the incidences of stroke and MI did not differ between the groups. It was, however, noted that concordant with prior data, ischemia-driven revascularization was higher at 5 years in the PCI group. Longer-term results from the EXCEL trial are awaited and will help guide future revascularization decisions.

NOBLE Trial

The Nordic-Baltic-British left main revascularization study (NOBLE) was a multicenter, prospective, randomized, noninferiority trial done across 36 centers in Europe. This trial included 1,184 patients with stable angina, unstable angina, or non-ST-elevation MI and randomized them to receive either CABG or PCI with biolimus-eluting biodegradable stents.[4] Patients with more than 3 additional coronary lesions or more complex coronary lesions, or considered at too high risk for CABG or PCI or with ST-elevation MI within 24 hours, and expected survival of less than 1 year, were excluded. The trial provided a direct comparison of the outcomes of patients with LM disease with different complexities treated either with CABG or with PCI. All patients, irrespective of their SYNTAX score (high, medium, or low), were included and treated with the intention of achieving complete revascularization of all vessels with significant lesions. While only patients with acute coronary syndrome in the CABG group received 75 mg of clopidogrel daily for 12 months, all patients in the PCI group received 75 mg of clopidogrel daily for 12 months. Treatment also included lifelong 75-to-150 mg of aspirin. It was hypothesized that PCI would produce no more inferior clinical outcomes than CABG in patients with unprotected LMCAD.[41] The primary endpoint was a composite of MACCE (death of any cause, nonprocedural MI repeat

revascularization, and stroke). Patients in both the treatment groups had similar age (66.2 years) and SYNTAX scores (22.4 in the PCI group and 22.3 in the CABG group). Even though the MACCE rates were similar between the 2 groups at 1 year (42 [7%] *v* 42 [7%]; 95% CI −2.9 to 2.9, p = 1.00), differences were evident after the first 12 months following the intervention. At 5 years,[42] rates of MACCE were higher with PCI (28% *v* 19% with CABG; p = 0.0002), and exceeded the noninferiority threshold [HR 1.58 (95% CI 1.24-2.01)], and was significant for superiority of CABG compared with PCI (p = 0.0044). All-cause mortality and cardiac death were similar after the 2 procedures (9% for both CABG and PCI; (HR 1.08, 95% CI 0.74-1.59; p = 0.68). However, patients treated with CABG had lower rates of nonprocedural MI (3% *v* 8% with PCI; p = 0.0002) and repeat revascularization (10% *v* 17% with PCI). SYNTAX score was not associated with adverse outcomes after PCI compared to CABG.[30,43]

Despite the fact that the patient population was largely similar between the NOBLE and EXCEL trials and the fact that both trials used second-generation drug-eluting stents, the 2 trials provided contradicting conclusions.[26] While the NOBLE trial showed that CABG was superior to PCI in the treatment of LM disease, the EXCEL trial reported noninferiority of PCI to CABG for the primary composite endpoint of MACCE. Of note, "repeat revascularization" was not a part of the composite of the primary outcome in the EXCEL trial. Moreover, the NOBLE trial included nonprocedural MI in preference to periprocedural MI used by other trials.

Summarized and tabulated trial data are shown in Table 2.

Retrospective Randomized Data

IRIS MAIN Study

In a retrospective observational study from the Left MAIN Revascularization (IRIS-MAIN) registry, the authors reported similar long-term risk of the composite primary outcomes of death, MI, or stroke between CABG and PCI.[44] The study adopted an "all-comers" design and included all consecutive Asian patients with significant unprotected LMCAD (defined as stenosis of >50%) undergoing either CABG or PCI without any concomitant valvular or aortic surgery. Out of 3,504 included patients, the primary outcome occurred in 7.5% patients in the PCI group *v* 11.9% patients in the CABG group (HR: 0.66; 95% CI 0.56-0.79; p < 0.001) at the end of 3 years. Even though the authors reported similar risks of the primary outcome in a propensity-matched cohort (PCI *v* CABG 9.6% *v* 9.9%; HR: 0.94; 95% CI: 0.77-1.15; p = 0.54), they found that the risks for MI (HR: 2.11; 95% CI: 1.16-3.83; p = 0.01) and repeat revascularization (HR: 5.95; 95% CI: 3.94-8.98; p <.001) were significantly higher in the PCI group. The findings from this study were consistent with that of the PRECOMBAT, SYNTAX, and EXCEL trials. However, this study was from a multicentric registry that did not allow for the consideration of variables, such as SYNTAX score and patient frailty during analysis of outcomes.

MAIN COMPARE Registry

The 10-year results of the MAIN-COMPARE registry were presented at the Transcatheter Therapeutics meeting in San Diego.[45] The 3-year and 5-year results of this observational study from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry have been previously published.[46,47] Briefly, the MAIN-COMPARE registry included patients with unprotected LMCAD (stenosis >50%) who underwent PCI or CABG at 12 major centers in Korea between January 2000 and June 2006. Exclusion criteria were patients with prior CABG, concomitant valvular or aortic surgery, or ST-segment elevation MI. During a 5-year follow-up, stenting was reported to have similar rates of mortality (HR 1.13; 95% CI: 0.88-1.44, p = 0.35) and of the composite of death, Q-wave MI, or stroke (HR: 1.07; 95% CI: 0.84-1.37, p = 0.59) but higher rates of target vessel revascularization (HR: 5.11; 95% CI: 3.52-7.42, p < 0.001) than CABG in patients with unprotected LMCAD. The authors further reported the 10-year outcomes of patients, with a loss of only 1.3% of patients to follow-up. There was again no significant difference in the unadjusted cumulative incidences of all-cause death and all-cause death, MI, or stroke between PCI and CABG after 10 years of revascularization (respectively, 21.1% *v* 23.2%; p = 0.23 and 23.8% *v* 26.3%; p = 0.13). Target vessel revascularization was lower after surgery compared with PCI (21.1% *v* 5.8%; p < 0.001). The results remained largely unchanged after propensity matching with similar risk of all-cause death and all-cause death, MI, or stroke between treatment groups within 5 years from index revascularization and from 5 to 10 years (0-5 years: HR 1.10, 95% CI 0.82-1.47; p = 0.53; 5-10 years: HR 1.09, 95% CI 0.87-1.36; p = 0.48; and 0-5 years: HR 0.98, 95% CI 0.75-1.29; p = 0.91; 5-10 years: HR 1.16, 95% CI 0.93-1.43; p = 0.19). However, when patients treated with DES were compared with the CABG patients, an excess of mortality and all-cause death, MI, or stroke from 5 to 10 years from index procedure was observed (respectively, HR 1.35, 95% CI 1.00-1.81; p = 0.05 and HR 1.46, 95% CI 1.10-1.94; p = 0.009). Therefore, the study did not observe any significant difference in the outcomes of mortality and a composite of death, Q-wave MI, or stroke between PCI and CABG up to 10 years. However, the results clearly showed a benefit of CABG over PCI with DES on mortality and a composite of death, Q-wave MI, or stroke after 5 years.

Meta-analyses

Several meta-analyses evaluating the outcomes of patients with LMCAD undergoing CABG and PCI have been published with differing conclusions.[48-54] A 2016 study analyzing the 5-year results of the PRECOMBAT and SYNTAX trials found that PCI was associated with significantly higher MACCE than CABG at 5 years (28.3% *v* 23.0%, p = 0.045).[48] In patients with isolated LM or LM with additional 1-vessel disease, PCI was associated with a 60% reduction in all-cause

Table 2
Summary of Trials With the Longest Follow-Up

	SYNTAX Trial[29]		NOBLE Trial[42]		EXCEL Trial[40]		PRECOMBAT Trial[45]		Le MANS Trial[33]	
	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG
Longest follow-up	10 years		5 years		5 years		10 years		10 years	
Region	Multicenter (North America, Europe)		North European countries		Multicenter (North America, Europe, others)		Hospitals in Korea		Multicenter (United States, Poland)	
Number of patients	Total patients followed up for 10 years (N = 841) LMCAD (N =357)	Total patients followed up for 10 years (N = 848 LMCAD (N = 348)	592	592	948	957	300	300	52 (23 followed up for 10 years)	53 (23 followed up for 10 years)
Mean age, y	65.2	65	66.2 years (IQR 9.9)	66.2 years (IQR 9.9)	66.0 ± 9.6	65.9 ± 9.5	61.8 ± 10.0	62.7 ± 9.5	60.6 ± 10.5	61.3 ± 8.4
SYNTAX Score	28.4	29.1	22 (SD 8)	22 (SD 7)	20.6 ± 6.2	20.5 ± 6.1	24.3 ± 9.6	25.3 ± 10.9	25.2 ± 8.7	24.7 ± 6.8
Type of Stent	First-generation, Paclitaxel-eluting stent		New generation umirolimus-eluting stent		Everolimus-eluting stents		Sirolimus-eluting stents		Drug-eluting stents (if reference diameter <3.8 mm), bare-metal stents (if diameter ≥3.8 mm)	
Outcomes										
Primary outcome	All-cause death		MACCE (all-cause mortality, non-procedural myocardial infarction, repeat revascularization, or stroke assessed after 5 years)		Composite of death from any cause, stroke or myocardial infarction		Major adverse cardiac or cerebrovascular events		Left ventricular ejection fraction	
	PCI 26.6% *v* CABG 28.2% HR 0.92 (95% CI 0.69-1.22), p = 0.023)		PCI 28% *v* CABG 19% (HR 1.58 [95% CI 1.24-2.01]; p = 0.0002)		PCI 22% *v* CABG 19.2% (HR 1/.10 [95% CI 0.95-1.50])		PCI 29.8% *v* CABG 24.7% (HR 1.25 [95% CI 0.93-1.69]		54.9 ± 8.3%	49.8 ± 10.3%
	(95/357)	(98/348)	(165/592)	(110/592)	(203/948)	(176/957)	(87/300)	(72/300)		
Death	See above	See above	PCI 9% *v* CABG 9% (HR 1.08 [95% CI 0.74-1.59]; p = 0.68)		PCI 13% *v* CABG 9.9% (HR 1.38 [95% CI 1.03-1.85])		PCI 14.5% *v* CABG 13.8% (HR 1.13 [95% CI 0.75-1.70])		PCI 21.6% *v* CABG 30.2% (HR 1.55 [95% CI 0.71-3.39]; p = 0.26)	
			(54/592)	(50/592)	(119/948)	(89/957)	(42/300)	(40/300)		
Stroke	-	-	PCI 4% *v* CABG 2% (HR 1.75 [95% CI 0.86-3.55]; p = 0.11)		PCI 2.9% *v* CABG 3.7% (HR 0.78 [95% CI 0.46-1.31])		PCI 1.9% *v* CABG 2.2% (HR 0.71 [95% CI 0.22-2.23])		PCI 4.3% *v* CABG 6.3% (HR 2.85 [95% CI 0.40-20.4]; p = 0.29)	
			(21/592)	(12/592)	(26/948)	(33/957)	(5/300)	(6/300)		
Repeat revascularization	-	-	PCI 17% *v* CABG 10% (HR 1.73; [95% CI 1.25-2.40]; p = 0.0009)		PCI 17.2% *v* CABG 10.5% (HR 1.79 [95% CI 1.36-2.36])		PCI 21.3% *v* CABG 10.6% (HR 2.04 [95% CI 1.33-3.11])		PCI 26.1% vs. CABG 31.3% (HR 1.34 [95% CI 0.61-2.95]; p = 0.46)	
			(97/592)	(58/592)	(153/948)	(92/957)	(59/300)	(29/300)		
Myocardial infarction	-	-	PCI 8% *v* CABG 3% (HR 2.99; [95% CI 1.66-5.39]; p = 0.0002)		PCI 10.6% *v* CABG 9.1% (HR 1.14 [95% CI 0.84-1.55])		PCI 3.2% *v* CABG 2.8% (HR 0.76 [95% CI 0.32-1.82])		PCI 8.7% *v* CABG 10.4% (HR 1.14 [95% CI 0.30-4.25]; p = 0.83)	
			(43/592)	(15/592)	(95/948)	(84/957)	(9/300)	(8/300)		

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; EXCEL, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; HR, hazard ratio; IQR, interquartile range; LE MANS, Left Main Coronary Artery Stenting; LMCAD, left main coronary artery disease; MACCE, major adverse cardiovascular and cerebrovascular event; NOBLE, Nordic-Baltic-British left main revascularization study; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SD, standard deviation; SYNTAX, Synergy between Percutaneous Coronary intervention with TAXUX and Cardiac surgery; TIMI, thrombolysis in myocardial infarction.

mortality (HR, 0.40; 95% CI 0.20-0.83; p = 0.029) and a 67% reduction in cardiac mortality (HR, 0.33; 95% CI 0.12-0.88; p = 0.025) when compared to CABG.[26] These results are in line with previously published literature.[53,54] Other studies have shown comparable outcomes in patients undergoing PCI and CABG.[49] A pooled analysis from 11 randomized trials found that the 5-year all-cause mortality was similar for patients with LMCAD undergoing PCI and CABG (10.7% after PCI *v* 10.5% after CABG; HR 1.07 [95% CI 0.87-1.33; p = 0.52]), regardless of diabetes status.[50] Another meta-analysis[51] looking at the 5-year outcomes of patients with unprotected LM disease concluded that there was no significant difference between PCI and CABG in all-cause (OR 0.93, [95% CI 0.71-1.21]) and cardiovascular mortality. Patients undergoing CABG had a reduced risk of MI, revascularization, and MACCE. More recently, Ahmad et al published the results of their meta-analysis[52] evaluating the results from all the trials comparing CABG and PCI. The study included the 1-year results from the study by Boudriot,[55] the 5-year results of the NOBLE,[42] EXCEL,[40] and PRECOMBAT[35] trials, and the 10-year results from the SYNTAX trial.[29] The mean follow-up duration was 67.1 months. The authors reported no significant differences between PCI and CABG for all-cause mortality (relative risk [RR] 1.03, [95% CI 0.81-1.32]; p = 0.779), cardiac death (RR 1.03, [95% CI 0.79-1.34]; p = 0.817), MI (RR 1.22, [95% CI 0.96-1.56]; p = 0.110) and stroke (RR 0.74, [95% CI 0.35-1.50]; p = 0.400). There was noted to be an increased risk of unplanned revascularization associated with PCI (RR 1.73, [95% CI 1.49-2.02]; p < 0.001).

Conclusion

CABG and PCI are both complimentary revascularization strategies for patients with stable LMCA disease. Individualized decision-making is needed considering the coronary anatomy, SYNTAX score, presence of co-existing cardiac and non-cardiac medical conditions, as well as patient preference. The involvement of a multidisciplinary team (or the Heart Team), including cardiac surgeons, interventional cardiologists, anesthesiologists, and cardiac imaging specialists, is paramount in decision-making.

Acknowledgments

The authors would like to thank Barbara Weisser, Mayo Clinic Academic Support Office, Scottsdale, Arizona, USA.

References

1 Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2014;64:1929–49.

2 Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619.

3 Khan MA, Hashim MJ, Mustafa H, et al. Global epidemiology of ischemic heart disease: Results from the Global Burden of Disease study. Cureus 2020;12:e9349.

4 Kindi HA, Samaan A, Hosny H. NOBLE and EXCEL: The debate for excellence in dealing with left main stenosis. Glob Cardiol Sci Pract 2018;2018:3.

5 Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.

6 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. Lancet 2002;360:7–22.

7 GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. Lancet 1994;343:1115–22.

8 Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791–800.

9 Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503–15.

10 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.

11 Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.

12 Conley MJ, Ely RL, Kisslo J, et al. The prognostic spectrum of left main stenosis. Circulation 1978;57:947–52.

13 Takaro T, Peduzzi P, Detre KM, et al. Survival in subgroups of patients with left main coronary artery disease. Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. Circulation 1982;66:14–22.

14 Ramadan R, Boden WE, Kinlay S. Management of left main coronary artery disease. J Am Heart Assoc 2018;7:e008151.

15 Fisher LD, Judkins MP, Lesperance J, et al. Reproducibility of coronary arteriographic reading in the coronary artery surgery study (CASS). Cathet Cardiovasc Diagn 1982;8:565–75.

16 Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. Circulation 2009;120:1505–12.

17 Hwang MH, Meadows WR, Palac RT, et al. Progression of native coronary artery disease at 10 years: Insights from a randomized study of medical versus surgical therapy for angina. J Am Coll Cardiol 1990;16:1066–70.

18 Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. Circulation 1999;99:2345–57.

19 de la Torre Hernandez JM, Baz Alonso JA, Gómez Hospital JA, et al. Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: Pooled analysis at the patient-level of 4 registries. JACC Cardiovasc Interv 2014;7:244–54.

20 Park S-J, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interv 2009;2:167–77.

21 Fearon WF, Yong AS, Lenders G, et al. The impact of downstream coronary stenosis on fractional flow reserve assessment of intermediate left main coronary artery disease: human validation. JACC Cardiovasc Interv 2015;8:398–403.

22 Nappi AG, Boden WE. Does physiology trump anatomy as the "best course" to guide PCI decision making and outcomes? J Am Coll Cardiol 2016;67:1712–4.

23 Serruys PW, Morice M-C, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.

24 Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation 2010;121:2645–53.

25 Morice MC, Serruys PW, Kappetein AP, et al. 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. Circulation 2014;129:2388–94.

26 Nagarajarao HS, Ojha CP, Mulukutla V, et al. Current use and trends in unprotected left main coronary artery percutaneous intervention. Curr Cardiol Rep 2020;22:16.

27 Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv 2012;79:453–95.

28 Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87–165.

29 Thuijs D, Kappetein AP, Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. Lancet 2019;394:1325–34.

30 Jahangiri M, Mani K, Yates MT, et al. The EXCEL trial: The surgeons' perspective. Eur Cardiol 2020;15:e67.

31 King SB 3rd, Smith SC Jr., Hirshfeld JW Jr., et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 writing group to review new evidence and update the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention, writing on behalf of the 2005 Writing Committee. Circulation 2008;117:261–95.

32 Yousif Ahmad CC. Left main stenting in 2020. Integrating EXCEL 5-year data into clinical practice. Cardiac Interventions Today 2020;14.

33 Buszman PE, Buszman PP, Banasiewicz-Szkróbka I, et al. Left main stenting in comparison with surgical revascularization: 10-year outcomes of the (Left Main Coronary Artery Stenting) LE MANS trial. JACC Cardiovasc Interv 2016;9(4):318–27.

34 Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol 2008;51:538–45.

35 Ahn J-M, Roh J-H, Kim Y-H, et al. Randomized trial of stents versus bypass surgery. J Am Coll Cardiol 2015;65:2198–206.

36 Park S-J, Kim Y-H, Park D-W, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med 2011;364:1718–27.

37 Park D-W, Ahn JM, Park H, et al. Ten-year outcomes after drug-eluting stents versus coronary artery bypass grafting for left main coronary disease: Extended follow-up of the PRECOMBAT trial. Circulation 2020;141:1437–46.

38 Park D-W, Ahn JM, Park S-J, et al. Percutaneous coronary intervention in left main disease: SYNTAX, PRECOMBAT, EXCEL and NOBLE-combined cardiology and cardiac surgery perspective. Ann Cardiothorac Surg 2018;7:521–6.

39 Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016;375:2223–35.

40 Stone GW, Kappetein AP, Sabik JF, et al. Five-year outcomes after PCI or CABG for left main coronary disease. N Engl J Med 2019;381:1820–30.

41 Gomes WJ, Albuquerque LC, Jatene FB, et al. The transfiguration of the EXCEL trial: Exceeding ethical and moral boundaries. Eur J Cardiothorac Surg 2020;58:30–4.

42 Holm NR, Mäkikallio T, Lindsay MM, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: Updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. Lancet 2020;395:191–9.

43 Doenst T, Bargenda S, Kirov H, et al. Cardiac surgery 2019 reviewed. Thorac Cardiovasc Surg 2020;68:363–76.

44 Lee PH, Lee JY, Lee CW, et al. Long-term outcomes of bypass grafting versus drug-eluting stenting for left main coronary artery disease: Results from the IRIS-MAIN registry. Am Heart J 2017;193:76–83.

45 Park DW, Ahn JM, Yun SC, et al. 10-year outcomes of stents versus coronary artery bypass grafting for left main coronary artery disease. J Am Coll Cardiol 2018;72:2813–22.

46 Seung KB, Park D-W, Kim Y-H, et al. Stents versus coronary-artery bypass grafting for left main coronary artery disease. N Engl J Med 2008;358:1781–92.

47 Park D-W, Seung KB, Kim Y-H, et al. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (revascularization for unprotected left main coronary artery stenosis: comparison of percutaneous coronary angioplasty versus surgical revascularization) registry. J Am Coll Cardiol 2010;56:117–24.

48 Cavalcante R, Sotomi Y, Lee CW, et al. Outcomes after percutaneous coronary intervention or bypass surgery in patients with unprotected left main disease. J Am Coll Cardiol 2016;68:999–1009.

49 Sardar P, Giri J, Elmariah S, et al. Meta-analysis of drug-eluting stents versus coronary artery bypass grafting in unprotected left main coronary narrowing. Am J Cardiol 2017;119:1746–52.

50 Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: A pooled analysis of individual patient data. Lancet 2018;391:939–48.

51 D'Ascenzo F, De Filippo O, Elia E, et al. Percutaneous vs. surgical revascularization for patients with unprotected left main stenosis: A meta-analysis of 5-year follow-up randomized controlled trials. Eur Heart J Qual Care Clin Outcomes 2021;16:476–85.

52 Ahmad Y, Howard JP, Arnold AD, et al. Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: A meta-analysis of randomized controlled trials. Eur Heart J 2020;41:3228–35.

53 Giacoppo D, Colleran R, Cassese S, et al. Percutaneous coronary intervention vs coronary artery bypass grafting in patients with left main coronary artery stenosis: A systematic review and meta-analysis. JAMA Cardiol 2017;2:1079–88.

54 Zhang XL, Zhu QQ, Yang JJ, et al. Percutaneous intervention versus coronary artery bypass graft surgery in left main coronary artery stenosis: A systematic review and meta-analysis. BMC Med 2017;15:84.

55 Boudriot E, Thiele H, Walther T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. J Am Coll Cardiol 2011;57:538–45.