Percutaneous Coronary Intervention of Left Main Disease

Pre- and Post-EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic-Baltic-British Left Main Revascularization Study) Era

Duk-Woo Park, MD, PhD; Seung-Jung Park, MD, PhD

Abstract—For nearly half a century, coronary artery bypass grafting has been the standard treatment for patients with obstructive left main coronary artery (LMCA) disease. However, there has been considerable evolution in the field of percutaneous coronary intervention, and especially, percutaneous coronary intervention for LMCA disease has been rapidly expanded with adoption of drug-eluting stents. Some, but not all randomized trials, have shown that percutaneous coronary intervention with drug-eluting stents might be a suitable alternative for selected patients with LMCA disease instead of bypass surgery. However, none of previous trials involving early-generation drug-eluting stents was sufficiently powered and comparative trials using contemporary drug-eluting stents were limited. Recently, primary results of 2 new trials of EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic-Baltic-British Left Main Revascularization Study) were reported. However, these trials showed conflicting results, which might pose uncertainty on the optimal revascularization strategy for LMCA disease. In this article, with the incorporation of a key review on evolution of LMCA treatment, we summarize the similarity or disparity of the EXCEL and NOBLE trials, focus on how they relate to previous trials in the field, and finally speculate on how the treatment strategy may be changed or recommended for LMCA treatment. **(*Circ Cardiovasc Interv*. 2017;10:e004792. DOI: 10.1161/CIRCINTERVENTIONS.117.004792.)**

Key Words: coronary artery bypass ■ coronary disease ■ percutaneous coronary intervention ■ stents

Because of the large extent of jeopardized myocardium, obstructive left main coronary artery (LMCA) disease is associated with high morbidity and mortality. Coronary artery bypass graft (CABG) surgery has long been the standard of care for patients with LMCA disease, whereas percutaneous coronary intervention (PCI) was only performed as salvage treatment. However, over time, the PCI treatment has undergone considerable therapeutic evolution. Remarkable advancements in stent technology, technical refinement, and adjunctive drug therapy have led to progressively improved PCI outcomes for LMCA disease.[1]

With such dramatic changes of PCI field, the optimal revascularization for LMCA disease has been the subject of numerous randomized clinical trials (RCT). In the early period of drug-eluting stents (DES), several RCT suggested that PCI achieved similar rates of mortality and serious composite outcome, but more frequent revascularization with PCI and more frequent stroke with CABG.[2–8] However, none of these trials have been adequately powered or have included contemporary second-generation metallic DES, which have a better safety and efficacy profile compared with the first-generation DES.[9,10] The long-awaited results of the 2 large-sized RCT, the EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and the NOBLE (Nordic-Baltic-British Left Main Revascularization Study), have been published.[11,12] However, the 2 trials showed conflicting results; EXCEL found that PCI is noninferior to CABG, whereas NOBLE shows that CABG is superior to PCI. This opposing finding may intensify the confusion in clinical decision making for optimal revascularization strategy. On this background, with understanding the evolution in LMCA treatment, we would like to focus on the cutting edge contemporary reviews of the recent trials, interpret how they relate to previous trials in the field, and speculate on the future direction for optimal LMCA management.

Historical Data for CABG Superiority

The natural prognosis of patients with medically treated LMCA disease was very poor; previous old data showed that 5-year rate of cardiac mortality was >50% in medically treated patients.[13] Since RCTs comparing CABG with medical therapy

Received February 27, 2017; accepted May 9, 2017.

From the Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

Correspondence to Seung-Jung Park, MD, PhD, Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Poongnap-dong, Songpa-gu, Seoul 138–736, Korea. E-mail sjpark@amc.seoul.kr

alone were conducted more than half a century ago,[14,15] CABG has been the first choice of care for LMCA disease. However, the VA (Veterans Administration) Cooperative Study involved only a subgroup of 113 patients with LMCA lesions (53 medical therapy and 60 CABG) and the ECSS (European Coronary Surgery Study) group study involved a subgroup of 59 patients with LMCA disease (31 medical therapy and 28 CABG). Although these results represented a subgroup of a subgroup and were hypothesis generating, the VA and ECSS study demonstrated that CABG was striking superior over medical therapy. Other historical observational studies also demonstrated a substantial benefit of CABG in patients with LMCA disease.[16,17] Since then, CABG has been always the treatment choice for a long time, and PCI was performed on a limited basis, mostly in surgically ineligible conditions.

Evolution in PCI for LMCA Disease

Coronary Stents

Although initial period of PCI with balloon angioplasty showed unsuccessful results, refinement of the technique and the introduction of coronary stents have led to progressively improved results. The adoption of metallic stents dramatically overcame inherent limitations of balloon angioplasty (ie, acute recoil, abrupt closure, or dissection) and rejuvenated interest in PCI for complex LMCA lesions. In the era of bare-metal stents, among elective low-risk patients, PCI with stenting showed acceptable in-hospital or midterm outcomes.[18–22] However, excessive risks of restenosis and repeat revascularization hampered the wide expansion of LMCA stenting. After a widespread use of DES with a lower risk of angiographic and clinical restenosis, PCI for LMCA disease has become much technically feasible and shows favorable short- and long-term clinical outcomes.[23–26] Since the introduction of the first-generation DES >10 years ago, the technology and engineering of DES have continuously advanced. The second-generation DES has adopted novel stent materials, thinner strut platforms, easy delivery system, and more biocompatible polymers (both durable and bioresorbable) than their predecessors.[27] Currently, newer-generation DES have become the default device; several observational studies have suggested similar or better outcomes with the second-generation DES compared with the first-generation ones for LMCA PCI.[28–30]

Imaging and Functional Tools

Accurate assessment of LMCA lesion is critical in determining PCI strategies and optimizing procedures. As stent technologies advance, there has been an evolution in invasive techniques that allow detailed assessment of both anatomy and function and an increased utilization of invasive imaging (intravascular ultrasound [IVUS]) or functional (fractional flow reserve [FFR]) tools.[31] The IVUS-guided PCI for LMCA disease has been an approach widely adopted in clinical practice. Although RCT data were not available, the prognostic value and stent optimization of LMCA PCI with IVUS have been examined in recent years.[32,33] Considering the benefits of IVUS to define disease distribution, inform stent sizing and technique, and enhance appropriate stent expansion, the role of IVUS in reducing LMCA restenosis and stent thrombosis-related complications may be clinically meaningful.

The decision about whether to treat the LMCA stenosis has already changed to include increased use of FFR.[34] Several observational studies demonstrated excellent survival and low event rates in medically treated patients with intermediate LMCA disease and a measured FFR value of >0.75–0.80,[35,36]; this value is generally accepted as a useful cutoff to determine a functionally significant LMCA stenosis. In the contemporary PCI practice, FFR-guided intervention can help to select appropriate patients and lesions for treatment, avoid unnecessary procedures, reduce medical costs, and improve clinical outcomes. In addition, an integrated use of IVUS and FFR might provide an interactive insight for evaluation of LMCA stenosis.[37] There is always ambiguity and conundrum of the FFR evaluation of LMCA stenosis and combined tandem lesions in the large side branch mitigating the ability to maximize hyperemia; IVUS may be an appropriate guide at this point and have a complementary role in functional evaluation of LMCA stenosis.

The angiographic SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score is a parameter derived to express the overall anatomic complexity and frequently used in decision making of revascularization for LMCA disease.[38,39] However, PCI has substantially evolved since completion of the SYNTAX trial,[40] in which the first-generation paclitaxel-eluting stent was used and disease severity was only assessed according to the angiogram alone without use of FFR or IVUS. Future role of this functional or imaging guidance for treatment of LMCA or multivessel coronary artery disease (CAD) should be further investigated through subsequent clinical trials.[41]

PCI Techniques and Adjunctive Pharmacotherapy

Alongside a revolution of stent devices, improved interventional techniques and adjunctive pharmacotherapy have progressively resulted in enhanced PCI outcomes for LMCA disease. Over time, there has been more experience and expertise for LMCA PCI and technical advances for PCI optimization. In the Interventional Research IRIS-MAIN registry (Incorporation Society-Left MAIN Revascularization), stenting technique for LMCA PCI has been more simplified.[1] For distal LMCA disease, although multiple techniques for complex stenting have been proposed, a simple strategy with provisional side-branch approach is the preferred strategy and this pattern is observed in the real-world practice. In cases requiring complex double stenting, improved stent design, and thinner strut dimensions, evolving 2-stenting techniques with continuous refinement may contribute to improved PCI outcomes after complex LMCA stenting.

In addition, concomitant development of adjunctive pharmacotherapy, involving periprocedural antithrombotic agents (eg, unfractionated heparin, low molecular weight heparin, glycoprotein IIb/IIIa inhibitor, fondaparinux, or bivalirudin), antiplatelet therapy (eg, ticlopidine, clopidogrel, prasugrel, or ticagrelor), statins (first-, second-, and third-generation statins), or other secondary preventive drugs might substantially contribute to improvement of PCI outcomes for LMCA disease.[1]

Previous Trials of PCI and CABG for LMCA Disease: Pre-EXCEL and NOBLE Era

Before EXCEL and NOBLE trial, 4 RCTs comparing PCI involving the first-generation DES and CABG were conducted.[2–8] Study design, key findings, and strength/weakness of each trial are summarized in Table 1.

In the left main subgroup of the SYNTAX trial,[4,5] there were no significant differences in the rates of primary end point of major adverse cardiac and cerebrovascular event (MACCE; 37% versus 31%), death (13% versus 15%), or myocardial infarction (MI; 8% versus 5%) between PCI and CABG up to 5 years. PCI patients had a lower stroke (2% versus 4%), but a higher revascularization (27% versus 16%) compared with CABG patients. According to the SYNTAX score terciles, there was no between-group difference in MACCE in the low (0–22) and intermediate (23–32) score groups, but MACCE was significantly higher after PCI in the high score (≥33) group. However, there were marked swings in mortality with the lowest group (<32) having much lower mortality with PCI (8% versus 15%) and a much higher mortality (21% versus 14%) in the higher score (≥33) group, reflecting the inherent limitation of subanalysis of a subgroup and a potential bias because of small numbers.

The PRECOMBAT trial (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) is a first, LMCA-specified, moderate-sized, RCT comparing DES and CABG.[7,8] Up to 5 years, the rates of MACCE (18% versus 14%), death (6% versus 8%), MI (2% versus 2%), or stroke (1% versus 1%) were similar between PCI and CABG. However, target-vessel revascularization occurred more common after PCI than after CABG (11% versus 6%).

The current European and US guidelines were primarily based on the prespecified subgroup of 705 patients with LMCA disease in the SYNTAX trial and also refer to the findings of the LEMANS trial (Left Main Coronary Artery Stenting; 100 patients), PRECOMBAT trial (600 patients), and Boudriot et al trial (201 patients).[38,39] Considering wide noninferiority margin and the limited power of these studies, overall results should be interpreted with caution and cannot be considered clinically directive. Also, none of trials have included contemporary second-generation DES with a better safety and efficacy profile. This clinical unmet need motivated 2 large-sized landmark trials of EXCEL and NOBLE.

EXCEL and NOBLE Trials

Similarity or Disparity Between Trial Design and Outcomes

Details of design, organization, and major findings of the EXCEL and NOBLE trial are summarized in Table 2. In the EXCEL trial, 1905 patients with LMCA disease and low or intermediate anatomic complexity (SYNTAX score ≤32) were randomly assigned to undergo CABG or PCI with a fluoropolymer-based, cobalt chromium, everolimus-eluting stent. In the NOBLE trial, 1201 patients with the left main CAD were randomly assigned to CABG or PCI (11% of the patients received a first-generation DES and the rest a biolimus-eluting stent). Although a SYNTAX score was not a prespecified inclusion criteria, the NOBLE trial excluded patients with >3 additional noncomplex lesions or complex additional coronary lesions (length >25 mm, chronic total occlusion, 2-stent bifurcation, calcified or tortuous vessel morphology). Two trials were not blinded, and a clinical and anatomic eligibility for both PCI and CABG was assessed by an interventional cardiologist and a cardiac surgeon at each participating site.

In the EXCEL trial, PCI was noninferior to CABG with respect to the primary composite end point of death, stroke, or MI at 3 years (15.4% versus 14.7%). The primary end

Table 1. Prior Trials of PCI Versus CABG for LMCA in the Era of the First-Generation DES

	Recruitment Period	n (PCI/CABG)	Longest Follow-Up, y	Primary End Point	Key Findings	Strength	Weakness
LEMANS[2,3]	2001–2004	52/53	10	Change in LVEF	Improvement in LVEF only with PCI, comparable rates of death, MI, stroke, or TVR at 1 and 5 y	First RCT comparing PCI and CABG for LM disease	Very small number of patients Surrogate primary end point DES used only in 35%
SYNTAX-Left MAIN[4,5]	2005–2007	357/348	5	Death, MI, stroke, or RR	PCI was noninferior to CABG at 1 and 5 y	First moderate-sized RCT, mainly used for the current guideline recommendation	Subgroup analysis, only hypothesis generating
Boudriot et al[6]	2003–2009	100/101	1	Cardiac death, MI, or TVR	PCI was inferior to CABG at 1 y	First RCT comparing sirolimus-eluting stents and CABG for LM disease	Limited sample size Lack of long-term follow-up Stroke was not included in end point
PRECOMBAT[7,8]	2004–2009	300/300	5	Death, MI, stroke, or TVR	PCI was noninferior to CABG at 1 and 5 y	First LM-specific, moderate-sized RCT comparing DES and CABG for LM disease	Noninferiority margin was wide Routine angiographic follow-up in the PCI group

CABG indicates coronary artery bypass grafting; DES, drug-eluting stents; LEMANS, left main coronary artery stenting; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; 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; RR, repeat revascularization; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; and TVR, target vessel revascularization.

Table 2. Key Study Features and Major Findings of EXCEL and NOBLE Trials

Design	EXCEL Trial[11]	NOBLE Trial[12]
Study features		
Study type	Multicenter (126 sites in North/South America, Europe, Asia Pacific), prospective, open-label, randomized, noninferiority design trial comparing PCI and CABG	Multicenter (36 sites in northern Europe), prospective, open-label, randomized, noninferiority design trial comparing PCI and CABG
Main inclusion criteria	Unprotected LMCA disease with angiographic DS >70%, as estimated visually, or 50%≤DS<70% with at least one of following: (1) noninvasive evidence of ischemia referable to LMCA lesion, (2) IVUS MLA ≤6.0 mm^2, or (3) FFR ≤0.80	Unprotected LMCA disease with angiographic DS >50%, as estimated visually, or FFR <0.8
Key exclusion criteria	SYNTAX score ≥33, prior PCI at left main (any time) or any other coronary artery (within 1 y), prior CABG, concomitant valvular or aortic surgery, CK-MB>normal or recent MI with CK-MB still elevated, left main reference vessel diameter <2.25 or >4.25 mm	STEMI within 24 h, >3 or complex additional coronary lesions (length >25 mm, chronic total occlusion, 2-stent bifurcation, calcified or tortuous vessel morphology), patient is too high risk for CABG or PCI, expected survival <1 y
Recruitment period	September 2010 to March 2014	December 2008 to January 2015
Follow-up period (median), y	3.0 (2.4–3.0)	3.1 (2.0–5.0)
No. of patients (PCI/CABG)	948/957	592/592
Stent type used for PCI	XIENCE cobalt chromium, everolimus-eluting stent	BioMatrix biolimus-eluting stent recommended since March 2010, but other CE-marked DES allowed
Major findings		
Primary end point	Composite of all-cause death, MI, or stroke	Composite rate of all-cause death, nonprocedural MI, repeat revascularization, or stroke
	15.4% in PCI and 14.7% in CABG at 3 y	28.9% in PCI and 19.1% in CABG at 5 y
	HR (95% CI), 1.00 (0.79–1.26)	HR (95% CI), 1.48 (1.11–1.96)
Death	8.2% in PCI and 5.9% in CABG at 3 y	11.6% in PCI and 9.5% in CABG at 5 y
	HR (95% CI), 1.34 (0.94–1.91)	HR (95% CI), 1.07 (0.67–1.72)
MI	Periprocedural and spontaneous MI was included	Nonprocedural MI was only included
	8.0% in PCI and 8.3% in CABG at 3 y	6.9% in PCI and 1.9% in CABG at 5 y
	HR (95% CI), 0.93 (0.67–1.28)	HR (95% CI), 2.88 (1.40–5.90)
Stroke	2.3% in PCI and 2.9% in CABG at 3 y	4.9% in PCI and 1.7% in CABG at 5 y
	HR (95% CI), 0.77 (0.43–1.37)	HR (95% CI), 2.25 (0.93–5.48)
Death, MI, or stroke	15.4% in PCI and 14.7% in CABG at 3 y	13% in PCI and 22% in CABG at 5 y
	HR (95% CI), 1.00 (0.79–1.26)	HR (95% CI), 1.47 (1.06–2.05)
Revascularization	12.9% in PCI and 7.6% in CABG at 3 y	16.2% in PCI and 10.4% in CABG at 5 y
	HR (95% CI), 1.72 (1.27–2.33)	HR (95% CI), 1.50 (1.04–2.17)
Death, MI, stroke, or revascularization	23.1% in PCI and 19.1% in CABG at 3 y	28.9% in PCI and 19.1% in CABG at 5 y
	HR (95% CI), 1.18 (0.97–1.45)	HR (95% CI), 1.48 (1.11–1.96)
Definite stent thrombosis or symptomatic graft occlusion	0.7% in PCI and 5.4% in CABG at 3 y	3% in PCI and 4% in CABG at 5 y
	HR (95% CI), 0.12 (0.05–0.28)	HR (95% CI), 0.59 (0.26–1.36)

CABG indicates coronary artery bypass grafting; CE, Conformite Europeenne; CI, confidence interval; CK-MB, creatine kinase-myocardial band; DES, drug-eluting stent; DS, diameter stenosis; EXCEL, Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FFR, fractional flow reserve; HR, hazard ratio; IVUS, intravascular ultrasound; LMCA, left main coronary artery, MI, myocardial infarction; MLA, minimal lumen area; NOBLE, Nordic-Baltic-British Left Main Revascularization Study; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

point events were less common after PCI than after CABG within 30 days (4.9% versus 7.9%), whereas fewer primary end point events occurred in the CABG group than in the PCI group between 30 days and 3 years. The rates of early MI and major periprocedural adverse events (ie, bleeding, infection, major arrhythmia, and renal failure) within 30 days were significantly lower with PCI than with CABG (3.9% versus 6.2% and 8.1% versus 23.0%, respectively), but ischemia-driven revascularization during follow-up was more frequent after PCI than after CABG (12.6% versus 7.5%). In overall, these

findings suggest that PCI offer an early safety advantage and CABG offer greater long-term durability.

In the NOBLE trial, the 5-year rate of the primary end point of MACCE (death, nonprocedural MI, repeat revascularization, or stroke) was significantly higher after PCI than after CABG (29% versus 19%). The 5-year rate of nonprocedural MI (7% versus 2%) and any revascularization (16% versus 10%) were also higher after PCI. Although a lower rate of stroke was observed after PCI than after CABG within 30 days (0% versus 0.7%), but an unexpected, the 5-year of stroke tended to be higher in PCI patients than in CABG patients (5% versus 2%). The 5-year rate of death was similar between PCI and CABG (12% versus 9%). PCI was always inferior to CABG irrespective of SYNTAX score.

Plausible Explanation of Conflicting Results of EXCEL and NOBLE

Unexpectedly, the opposing results from 2 novel RCTs raise uncertainty rather than clarity with regard to the relative safety and effectiveness of PCI versus CABG for LMCA revascularization. Careful review and interpretation of this discrepancy may be helpful to understand and apply the trial findings for optimal LMCA treatment in the clinical practice. Plausible explanations of conflicting results could be (1) substantial between-study differences in patient assessment, risk profiles, trial process, or procedural characteristics, (2) a differential adoption of the primary composite end point, (3) an interstudy heterogeneity for the definition of MI, and (4) an unexplained higher risk of stroke after PCI in NOBLE.

At first, the integrated and skilled heart team approach, which was evident in EXCEL (but not in NOBLE), might influence a fair assessment for eligibility and cause the difference of patient's characteristics enrolled in trials. Also, the particulars of clinical practice in the participating sites and the specific expertise of the interventional cardiologists and cardiac surgeons who performed the procedures may influence the comparative outcomes after LMCA revascularization. A careful process of participating site selection might be a key component ensuring that the majority of patients with unprotected LMCA disease were equally treated well by means of 2 strategies of revascularization. In addition, differences in population size or follow-up might influence the conflicting results. In the NOBLE, there was interim change in the protocol and primary outcome reporting with extension of follow-up owing to lower than expected MACCE rates; this drawback may influence trial integrity and internal validation.

As a primary stent device, EXCEL used a thin-strut, fluoropolymer-based cobalt chromium, everolimus-eluting stents, which was associated with the lowest risk of stent thrombosis of all available DES.[42] In contrast, NOBLE used first-generation, thicker-strut, stainless steel, sirolimus-eluting Cypher stent (11%) or the biolimus-eluting Biomatrix Flex stent (89%). In both trials, there was a substantial difference in rates of definite stent thrombosis (0.7% in the EXCEL and 3% in the NOBLE); as a result, the rate of definite stent thrombosis or symptomatic graft occlusion was much higher after CABG than after PCI (5.4% versus 0.7%) in EXCEL, but similar (4% versus 3%) in NOBLE.

The EXCEL trial was the only trial adequately powered to assess the hard safety end points as the primary outcome measure, not including revascularization. It has been debated for long time that the risk of repeat revascularization can be equally balanced against the risk of death, MI, or stroke. Previous SYNTAX trial showed that the increase in the rate of repeat revascularization with PCI as compared with CABG did not seem to translate into a significant overall increase in the rate of death or MI.[40] By contrast, the NOBLE trials included repeat revascularization in the primary composite end point. As such, conflicting primary results between the EXCEL and the NOBLE trial are largely driven by differential defining primary composite end point.

In trials comparing PCI and CABG, the composite primary end point is sensitive to the definition of each event. For most of the trials, the definitions of death and stroke were similar. However, the protocol definition of MI was mostly different in RCTs comparing PCI and CABG for LMCA disease[2,4,6,7,11,12] and in several expert consensus documents[43–45] (Table 3). Owing to interstudy heterogeneity for MI definition, trial results can vary widely and this disparity can lead to an imprecise estimate of the overall treatment effect. Regardless of any symptom, sign, or ECG criteria, an increase of creatine kinase-myocardial band >10× the upper reference limit was considered as MI events in EXCEL, but not in NOBLE. The NOBLE trial did not routinely collect data on periprocedural MI (eg, procedural MI was only assessable in 45% of patients). Post-procedural increases of cardiac enzyme might be more common after CABG than after PCI because of more extensive manipulation and procedural features; thus, less stringent defining of periprocedural MI based on isolated creatine kinase-myocardial band elevation without additional electrocardiographic, imaging, or angiographic evidence may induce an unbalanced detection of periprocedural MI after CABG or PCI. Whether clinically driven MI is only considered or biomarker-driven MI without ischemic symptoms or signs is also included as a relevant clinical end point is not yet clearly determined. Because uniform definition of MI not penalizing one of the revascularization approaches is still lacking, additional studies and efforts by trialists are warranted to improve standardization of MI definition for future clinical trials comparing PCI and CABG.

Unexpectedly, the 5-year risk of stroke was more than twice higher after PCI rather than after CABG in NOBLE, which was the opposite to the results of EXCEL. A higher stroke risk after CABG was consistently observed in the SYNTAX and FREEDOM trials (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease).[40,46] Several meta-analyses also showed similar findings.[47–49] Because a greater rate of late stroke after PCI in NOBLE lacks biological plausibility and clear explanation for such a contradictory finding in NOBLE is still lacking, this result is most likely because of chance effect.[50]

Representativeness and Generalizability of EXCEL and NOBLE

In the clinical viewpoint, assessing the representativeness and generalizability of patients enrolled in trials compared with the real-world population is likely to be of considerable interest.

Table 3. Various Definition of Myocardial Infarction Used in Trials Comparing PCI and CABG for Left Main Disease and Used in the Expert Consensus Documents

Criteria	PCI	CABG	Observed/Expected MI Rates
By each trial			Observed MI rates
LEMANS[2]	CK-MB >3× the URL	CK-MB >5× the URL	1 patient in PCI (n=52) and 3 patients in CABG (n=53)
SYNTAX-Left MAIN[4]	Periprocedural (<7 d after intervention): new Q waves and either peak CK-MB/total CK >10% or CK-MB >5× the URL	Identical definition used	4.3% in PCI and 4.1% in CABG at 1 y
	Spontaneous (≥7 d after intervention): new Q waves or peak CK-MB/total CK >10% or CK-MB >5× the URL or CK >5× the URL		
Boudriot et al[6]	CK-MB >3× the URL and standard ECG criteria	CK-MB >5× the URL and standard ECG criteria	3% in PCI and 3% in CABG at 1 y
PRECOMBAT[7]	Periprocedural (≤2 d after intervention): new Q waves and increase in the CK-MB>5× the URL	Identical definition used	1.3% in PCI and 1.0% in CABG at 1 y
	Spontaneous (>2 d after intervention): new Q waves or CK-MB> the URL, plus ischemic symptoms or signs		
EXCEL[11]	Periprocedural (≤3 d after intervention): CK-MB >10× the URL, or CK-MB >5× the URL plus new pathological Q waves or LBBB, or new native or graft vessel occlusion, or imaging evidence of loss of viable myocardium or new regional wall motion abnormality	Identical definition used	8.0% in PCI and 8.3% in CABG at 3 y
	Spontaneous (>3 d after intervention): CK-MB or troponin >1 URL plus ischemic ECG changes, or pathological Q waves, or new native or graft vessel occlusion, or imaging evidence of loss of viable myocardium or new regional wall motion abnormality		
NOBLE[12]	Periprocedural: disregarded in primary composite end point	Identical definition used	6.9% in PCI and 1.9% in CABG at 5 y
	Spontaneous: CK-MB or troponin >1 time the URL with at least one of the following: (1) ischemic symptoms, (2) ischemic ECG changes; or (3) pathological Q wave		
By expert consensus document			Expected MI rates
Second universal definition[43]	Periprocedural: cardiac biomarker (troponin or CK-MB) >3× the URL	Periprocedural: cardiac biomarker (troponin or CK-MB) >5× the URL and any of the following: new pathological Q waves or LBBB, new native or graft vessel occlusion, imaging evidence of loss of viable myocardium	Periprocedural MI events may be much common after PCI than after CABG
	Spontaneous: cardiac biomarker (troponin or CK-MB) >1× the URL with at least one of the following: (1) ischemic symptoms, (2) ischemic ECG changes, (3) pathological Q wave, or (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality	Spontaneous: identical definition used	
Third universal definition[44]	Periprocedural: cardiac biomarker (preferably cardiac troponin) >5× the URL or a rise >20% if the baseline values are elevated and are stable or falling, and any of the following: (1) ischemic symptoms, (2) new ischemic ECG changes, (3) angiographic findings consistent with a procedural complication, or (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.	Periprocedural: cardiac biomarker (preferably cardiac troponin) >10× the URL or a rise >20% if the baseline values are elevated and are stable or falling, and any of the following: (1) pathological Q wave or new LBBB, (2) new graft or native vessel occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.	Overall rates of periprocedural MI after PCI or CABG may be low compared to other criteria. Periprocedural MI events may be slightly common after PCI than after CABG.

(*Continued*)

Table 3. Continued

Criteria	PCI	CABG	Observed/Expected MI Rates
	Spontaneous: cardiac biomarker (preferably cardiac troponin) >1× the URL with at least one of the following: (1) ischemic symptoms, (2) ischemic ECG changes, (3) pathological Q wave, (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or (5) intracoronary thrombus by angiography or autopsy	Spontaneous: identical definition used	
SCAI definition[45]	Periprocedural (≤48 h after intervention): CK-MB >10× the URL, or CK-MB >5× the URL with new pathological Q waves or new persistent LBBB. In the absence of CK-MB, troponin >70× the URL, or troponin >35× the URL with new pathological Q waves or new persistent LBBB	Identical definition used	Periprocedural MI events may be much common after CABG than after PCI
	Spontaneous (>48 d after intervention): CK-MB or troponin >1 URL plus ischemic ECG changes, or pathological Q waves, or new native or graft vessel occlusion, or imaging evidence of loss of viable myocardium or new regional wall motion abnormality		

CABG indicates coronary artery bypass grafting; CK-MB, creatine kinase-myocardial band; EXCEL, Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; LBBB, left bundle branch block; LEMANS, Left Main Coronary Artery Stenting; MI, myocardial infarction; 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; SCAI, Society for Cardiovascular Angiography and Interventions; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; and URL, upper reference limit.

Key clinical and procedural characteristics of patients in EXCEL and NOBLE and of those in the second-generation DES era of all-comers IRIS-MAIN registry[1] are summarized in Table 4. Approximately one third of patients in EXCEL and IRIS-MAIN had diabetes mellitus, but the proportion of diabetes mellitus was substantially lower in NOBLE. In addition, the proportion of patients with acute coronary syndrome was substantially lower in NOBLE. Patients with more complex CAD were more common in IRIS-MAIN (especially, in the CABG group).

With regard to procedural or operative characteristics, total stent number and total stent length in PCI patients were similar between RCTs and registry. In EXCEL and NOBLE, >70% of patients underwent IVUS-guided PCI, which was similar to IRIS-MAIN. In the CABG stratum, there was a significant difference in operative characteristics between trials and registry. The proportion of patients who underwent off-pump surgery was substantially lower in EXCEL and NOBLE than in IRIS-MAIN. The internal mammary artery was used in >90% of patients in both RCTs and registry, but the use of radial artery was <10% of patients in RCTs (saphenous vein grafts were more commonly used in trials), but >30% in the registry; thus, it is argued that the operative practice in trials is probably less representative of real-world practice. Although recent CABG trials suggest that a higher arterial revascularization with bilateral internal mammary artery and off-pump CABG would not have any difference to the outcome,[51,52] further investigation is required to evaluate how the surgical approach influence comparative outcomes in trials of PCI and CABG.

Role of SYNTAX Score

To date, several scoring systems have been developed for risk stratification and decision making of optimum revascularization strategy in patients with multivessel CAD with or without LMCA disease.[4,40,53,54] However, easy application of these scoring systems in clinical practice might be hampered because of limited clinical performance and complexities. Also, it is noted that the SYNTAX score (CAD extent) is not of major importance in the EXCEL and NOBLE trials.

In EXCEL, considerable difference of SYNTAX score by site assessment and angiographic core laboratory assessment exists. The SYNTAX score was underestimated at local sites. Thus, although the investigators recruited only patients with low and intermediate SYNTAX scores, 24.3% of randomized population (25.1% of PCI patients and 23.4% of CABG patients) had a high SYNTAX score according to the angiographic core laboratory analysis. Such finding might suggest that if the decision making between CABG and PCI was solely based on the anatomic SYNTAX score, the optimum revascularization method can be inconsistently shifting in a quarter of patients with LMCA disease with regard to interventional and surgical appropriateness and eligibility. In addition, there was no remarkable and discriminating interaction between SYNTAX score and revascularization type on clinical outcomes, contrast to the results of the original SYNTAX study.[4,5,40]

In NOBLE, the predictive and discriminative capacity of the SYNTAX score was much poor. The SYNTAX score was not associated with adverse outcomes after PCI or CABG. In particular, the unexpected finding of a substantially better outcome after CABG than after PCI in the low SYNTAX score group was found, suggesting a limited predictability of comparative outcomes by this score. These findings in the EXCEL and NOBLE trials may represent a limitation of the SYNTAX score for optimal decision making of revascularization strategies in patients with LMCA disease. Therefore, the clinical and practical usefulness of the SYNTAX score for treatment of patients with LMCA disease should be further debated.

Updated Meta-Analysis and Guideline Recommendation

Meta-Analysis

After publication of EXCEL and NOBLE trials, subsequent meta-analyses have been reported.[55,56] Nerlekar et al[55]

Table 4. Comparison of Baseline Characteristics of Randomized Patients in EXCEL and NOBLE With Real-World Patients in IRIS-MAIN

	PCI Patients			CABG Patients		
Key Baseline Variables	EXCEL (n=948)	NOBLE (n=592)	IRIS-MAIN (n=1707)	EXCEL (n=957)	NOBLE (n = 592)	IRIS-MAIN (n = 774)
Patient characteristics						
Age (mean, y)	66	66	64	66	66	65
Male sex (%)	76	80	78	78	76	80
Diabetes mellitus (%)	30	15	34	28	15	42
Previous PCI (%)	18	20	15	16	20	13
Clinical indication (%)						
Stable angina or silent ischemia	61	82	41	61	83	44
Acute coronary syndrome	39	18	59	40	17	57
Ejection fraction (mean or median)	57	60 (median)	59	57	60 (median)	55
CAD extent						
LM only	17	NA	11	18	NA	3
LM plus 1-vessel disease	31	NA	26	31	NA	6
LM plus 2-vessel disease	35	NA	36	32	NA	20
LM plus 3-vessel disease	17	NA	27	19	NA	71
LM location (%)						
Ostium or shaft	18	19	33	21	19	28
Distal bifurcation	82	81	67	79	81	73
PCI characteristics						
Total stent number (mean or median)	2.4	2 (median)	2.2	…	…	…
Total stent length (mean or median)	49	52 (median)	52	…	…	…
IVUS guidance, %	77	74	77	…	…	…
DES type, %						
CoCr-EES	98	…	37	…	…	…
BES	…	89	8	…	…	…
PtCr-EES	…	…	22	…	…	…
Re-ZES	…	…	27	…	…	…
PC-ZES	…	…	2	…	…	…
Other second DES	…	…	4	…	…	…
SES	…	11	…	…	…	…
CABG characteristics						
Off-pump surgery, %	…	…	…	29	16	69
No. of conduits (mean)	…	…	…	2.6	2.5	2.9
Use of internal mammary artery, %	…	…	…	99	93	94
Use of radial artery, %	…	…	…	6	5	37

BES indicates biolimus-eluting stent(s); CABG, coronary artery bypass graft; CAD, coronary artery disease; CoCr-EES, cobalt chromium, everolimus-eluting stent(s); DES, drug-eluting stents; EXCEL, Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; IRIS-MAIN, Interventional Research Incorporation Society-Left MAIN Revascularization; IVUS; intravascular ultrasound; LM, left main; NA, not available; NOBLE, Nordic-Baltic-British Left Main Revascularization Study; PC-ZES, phosphorylcholine polymer–based zotarolimus-eluting stent(s); PtCr-EES, platinum chromium everolimus-eluting stent(s); Re-ZES, resolute zotarolimus-eluting stent(s); and SES, sirolimus-eluting stent(s).

performed a meta-analysis of 5 RCT (Boudriot et al, PRECOMBAT, SYNTAX, NOBLE, and EXCEL). This study reported that the primary safety end point of death, MI, and stroke was similar between PCI and CABG (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.79–1.17; *P*=0.73). The individual component of death (OR, 1.03; 95% CI, 0.78–1.35;

P=0.61), MI (OR, 1.46; 95% CI, 0.88–2.45; *P*=0.08), and stroke (OR, 0.88; 95% CI, 0.39–1.97; *P*=0.53) was also similar, but PCI was associated with higher rates of repeat revascularization (OR, 1.85; 95% CI, 1.53–2.23; *P*<0.001). Upadhaya et al[56] performed a similar meta-analysis involving 5 trials. They reported that MACCE (death, MI, stroke, or repeat revascularization) (OR, 1.36; 95% CI, 1.18–1.58; *P*<0.001) and repeat revascularization (OR, 1.85; 95% CI, 1.53–2.23; *P*<0.001) was significantly higher after PCI than after CABG. Especially, based on SYNTAX score, CABG was superior with regard to MACCE only in the subgroup with SYNTAX score of ≥33. There were no significant differences in the incidence of MI, stroke, or cardiac and all-cause mortality.

Guideline Updates

On the basis of cumulative evidence of comparative effectiveness studies of LMCA revascularization, guideline recommendation for LMCA PCI has been less stringent.[1] In current 2014 European and U.S. guidelines,[38,39] CABG is a class of recommendation/Level of Evidence I B for LM revascularization and PCI is a I B, IIa B, or III B based on the SYNTAX score tertile. After recent publication of new landmark trials, should the revascularization guidelines change on the basis of the results of this trial? Although a dramatic change in class of recommendation for LMCA PCI is rarely expected, these trials provide additional evidence that may influence current guidelines by proposing less restrictive PCI indication and by expanding the patient pool that might be eligible for PCI. Also, given that SYNTAX score was not important factor to guide decision making for optimal revascularization and to differentiate the comparative outcomes between CABG and PCI in EXCEL and NOBLE, it may be further debated whether the SYNTAX score can work as the pivotal factor in the future revascularization guidelines.

Future Perspective

In the contemporary real-world practice, although clinical equipoise was present for either PCI or CABG, patients with less complex clinical and anatomic characteristics (ie, isolated left main disease, ostial or shaft left main disease, or additional noncomplex one- or two-vessel disease) might be preferentially treated by PCI rather than by CABG. The fact that >60% of patients are eligible for PCI in the EXCEL screening registry suggests that the practical threshold in choosing PCI for LMCA disease is likely to be less stringent in the clinical practice. In addition, the rate of primary end point was similar between PCI and CABG even in 24% of the patients with a high SYNTAX score (as measured by the angiographic core laboratory) of the EXCEL. However, although PCI with contemporary DES is less restrictively considered for a wide range of anatomic complexity, further studies are required to determine whether PCI is an acceptable alternative to CABG in patients with high anatomic complexity of LMCA disease.

Another noteworthy finding of EXCEL and NOBLE was a substantial interaction between treatment effect and time for the risk of major adverse events—late catch-up (in EXCEL) or late divergence (in NOBLE) in treatment effect of CABG over of PCI during long-term follow-up. Until recently, long-term follow-up studies up to 5 to 10 years are still limited.[57,58] Limited follow-up could have penalized the CABG group because the long-term benefits of CABG over PCI have not typically been fully evident until 5 to 10 years after the procedure. In addition, whether treatment differences between PCI and CABG will continue to accrue or diverge or are attenuated

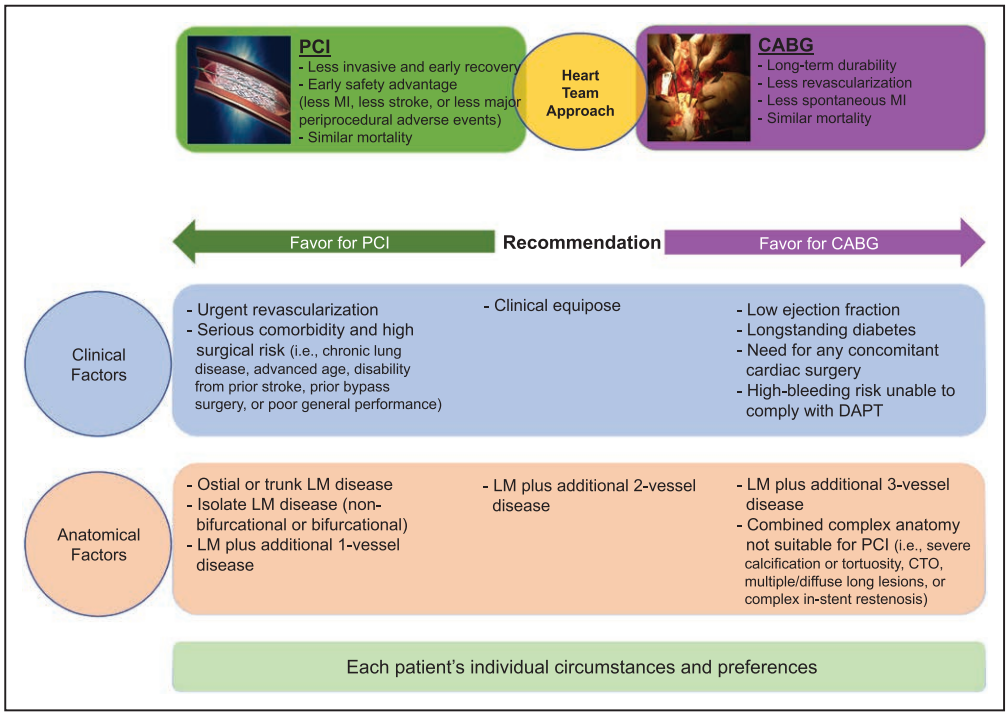

Figure. CABG indicates coronary artery bypass graft; CTO, chronic total occlusion; DAPT, dual antiplatelet therapy; LM, left main; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

by degenerative saphenous vein graft disease with longer-term follow-up deserves further investigation. Study patients in EXCEL and NOBLE will be followed up at 5 and 10 years, which will add additional valuable information.

In addition, as large-sized RCTs comparing PCI versus CABG for patients with LMCA disease are unlikely to be performed in the near future, further analyses in EXCEL and NOBLE and new meta-analysis represent the most updated and comprehensive evidence base to inform clinical decision making for the treatment of unprotected LMCA disease.

Summary

Over the several decades, there has been a remarkable evolution in surgical or percutaneous part of revascularization for patients with LMCA disease. The new results of EXCEL and NOBLE trials not only add to the level of evidence for optimal management of LMCA disease but also reposition the therapeutic role of each revascularization approach. There might be no clear-cut (all-or-none) right answer about the optimal revascularization strategy (Figure); some patients might prefer CABG surgery, and some patients might prefer PCI. The Heart Team approach may also have the relevant role in the individual patient decision making and for patient-centered care. Finally, the optimal choice of revascularization modality for LMCA disease should be made after discussion among the heart team members for determining appropriateness and eligibility of PCI or CABG and take into account the specific circumstances of each patient and individual preferences.

Disclosures

None.

References

1. Lee PH, Ahn JM, Chang M, Baek S, Yoon SH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park DW, Park SJ. Left main coronary artery disease: secular trends in patient characteristics, treatments, and outcomes. *J Am Coll Cardiol*. 2016;68:1233–1246. doi: 10.1016/j.jacc.2016.05.089.
2. Buszman PE, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, Bialkowska B, Dudek D, Gruszka A, Zurakowski A, Milewski K, Wilczynski M, Rzeszutko L, Buszman P, Szymszal J, Martin JL, Tendera M. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol*. 2008;51:538–545. doi: 10.1016/j.jacc.2007.09.054.
3. Buszman PE, Buszman PP, Banasiewicz-Szkróbka I, Milewski KP, Żurakowski A, Orlik B, Konkolewska M, Trela B, Janas A, Martin JL, Kiesz RS, Bochenek A. 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;9:318–327. doi: 10.1016/j.jcin.2015.10.044.
4. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR, Torracca L, van Es GA, Leadley K, Dawkins KD, Mohr F. 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;121:2645–2653. doi: 10.1161/CIRCULATIONAHA.109.899211.
5. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, Religa G, Huang J, Roy K, Dawkins KD, Mohr F. 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;129:2388–2394. doi: 10.1161/CIRCULATIONAHA.113.006689.
6. Boudriot E, Thiele H, Walther T, Liebetrau C, Boeckstegers P, Pohl T, Reichart B, Mudra H, Beier F, Gansera B, Neumann FJ, Gick M, Zietak T, Desch S, Schuler G, Mohr FW. 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;57:538–545. doi: 10.1016/j.jacc.2010.09.038.
7. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Chung CH, Lee JW, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med*. 2011;364:1718–1727. doi: 10.1056/NEJMoa1100452.
8. Ahn JM, Roh JH, Kim YH, Park DW, Yun SC, Lee PH, Chang M, Park HW, Lee SW, Lee CW, Park SW, Choo SJ, Chung C, Lee J, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB, Park SJ. Randomized trial of stents versus bypass surgery for left main coronary artery disease: 5-year outcomes of the PRECOMBAT study. *J Am Coll Cardiol*. 2015;65:2198–2206. doi: 10.1016/j.jacc.2015.03.033.
9. Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, Feit F, Bhatt DL, Slater J. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation*. 2012;125:2873–2891. doi: 10.1161/CIRCULATIONAHA.112.097014.
10. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, Vlachojannis GJ, Jensen LO, Christiansen EH, Berencsi K, Valgimigli M, Orlandi C, Petrou M, Rapezzi C, Stone GW. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol*. 2015;65:2496–2507. doi: 10.1016/j.jacc.2015.04.017.
11. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogáts G, Mansour S, Noiseux N, Sabaté M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Pagé P, Dressler O, Kosmidou I, Mehran R, Pocock SJ, Kappetein AP; EXCEL Trial Investigators. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med*. 2016;375:2223–2235. doi: 10.1056/NEJMoa1610227.
12. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, Trovik T, Eskola M, Romppanen H, Kellerth T, Ravkilde J, Jensen LO, Kalinauskas G, Linder RB, Pentikainen M, Hervold A, Banning A, Zaman A, Cotton J, Eriksen E, Margus S, Sørensen HT, Nielsen PH, Niemelä M, Kervinen K, Lassen JF, Maeng M, Oldroyd K, Berg G, Walsh SJ, Hanratty CG, Kumsars I, Stradins P, Steigen TK, Fröbert O, Graham AN, Endresen PC, Corbascio M, Kajander O, Trivedi U, Hartikainen J, Anttila V, Hildick-Smith D, Thuesen L, Christiansen EH; NOBLE Study Investigators. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet*. 2016;388:2743–2752. doi: 10.1016/S0140-6736(16)32052-9.
13. Bruschke AV, Proudfit WL, Sones FM, Jr. Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5-9 years. II. Ventriculographic and other correlations. *Circulation*. 1973;47:1154–1163.
14. Takaro T, Hultgren HN, Lipton MJ, Detre KM. The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. *Circulation*. 1976;54(6 suppl):III107–III117.
15. European Coronary Surgery Study Group. Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. *Lancet*. 1982;2:1173–1180.
16. Chaitman BR, Fisher LD, Bourassa MG, Davis K, Rogers WJ, Maynard C, Tyras DH, Berger RL, Judkins MP, Ringqvist I, Mock MB, Killip T. Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease. Report of the Collaborative Study in Coronary Artery Surgery (CASS). *Am J Cardiol*. 1981;48:765–777.
17. Campeau L, Corbara F, Crochet D, Petitclerc R. Left main coronary artery stenosis: the influence of aortocoronary bypass surgery on survival. *Circulation*. 1978;57:1111–1115.
18. Park SJ, Park SW, Hong MK, Cheong SS, Lee CW, Kim JJ, Hong MK, Mintz GS, Leon MB. Stenting of unprotected left main coronary artery stenoses: immediate and late outcomes. *J Am Coll Cardiol*. 1998;31:37–42.
19. Silvestri M, Barragan P, Sainsous J, Bayet G, Simeoni JB, Roquebert PO, Macaluso G, Bouvier JL, Comet B. Unprotected left main coronary artery

stenting: immediate and medium-term outcomes of 140 elective procedures. *J Am Coll Cardiol*. 2000;35:1543–1550.
20. Park SJ, Hong MK, Lee CW, Kim JJ, Song JK, Kang DH, Park SW, Mintz GS. Elective stenting of unprotected left main coronary artery stenosis: effect of debulking before stenting and intravascular ultrasound guidance. *J Am Coll Cardiol*. 2001;38:1054–1060.
21. Black A, Cortina R, Bossi I, Choussat R, Fajadet J, Marco J. Unprotected left main coronary artery stenting: correlates of midterm survival and impact of patient selection. *J Am Coll Cardiol*. 2001;37:832–838.
22. Takagi T, Stankovic G, Finci L, Toutouzas K, Chieffo A, Spanos V, Liistro F, Briguori C, Corvaja N, Albero R, Sivieri G, Paloschi R, Di Mario C, Colombo A. Results and long-term predictors of adverse clinical events after elective percutaneous interventions on unprotected left main coronary artery. *Circulation*. 2002;106:698–702.
23. Park SJ, Kim YH, Lee BK, Lee SW, Lee CW, Hong MK, Kim JJ, Mintz GS, Park SW. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. *J Am Coll Cardiol*. 2005;45:351–356. doi: 10.1016/j.jacc.2004.10.039.
24. Valgimigli M, van Mieghem CA, Ong AT, Aoki J, Granillo GA, McFadden EP, Kappetein AP, de Feyter PJ, Smits PC, Regar E, Van der Giessen WJ, Sianos G, de Jaegere P, Van Domburg RT, Serruys PW. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). *Circulation*. 2005;111:1383–1389. doi: 10.1161/01.CIR.0000158486.20865.8B.
25. Chieffo A, Park SJ, Valgimigli M, Kim YH, Daemen J, Sheiban I, Truffa A, Montorfano M, Airoldi F, Sangiorgi G, Carlino M, Michev I, Lee CW, Hong MK, Park SW, Moretti C, Bonizzoni E, Rogacka R, Serruys PW, Colombo A. Favorable long-term outcome after drug-eluting stent implantation in nonbifurcation lesions that involve unprotected left main coronary artery: a multicenter registry. *Circulation*. 2007;116:158–162. doi: 10.1161/CIRCULATIONAHA.107.692178.
26. Chieffo A, Stankovic G, Bonizzoni E, Tsagalou E, Iakovou I, Montorfano M, Airoldi F, Michev I, Sangiorgi MG, Carlino M, Vitrella G, Colombo A. Early and mid-term results of drug-eluting stent implantation in unprotected left main. *Circulation*. 2005;111:791–795. doi: 10.1161/01.CIR.0000155256.88940.F8.
27. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med*. 2013;368:254–265. doi: 10.1056/NEJMra1210816.
28. Valenti R, Migliorini A, Parodi G, Carrabba N, Vergara R, Dovellini EV, Antoniucci D. Clinical and angiographic outcomes of patients treated with everolimus-eluting stents or first-generation Paclitaxel-eluting stents for unprotected left main disease. *J Am Coll Cardiol*. 2012;60:1217–1222. doi: 10.1016/j.jacc.2012.05.038.
29. Kim YH, Park DW, Ahn JM, Yun SC, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Jang Y, Jeong MH, Kim HS, Hur SH, Rha SW, Lim DS, Her SH, Seung KB, Seong IW, Park SJ; PRECOMBAT-2 Investigators. Everolimus-eluting stent implantation for unprotected left main coronary artery stenosis. The PRECOMBAT-2 (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) study. *JACC Cardiovasc Interv*. 2012;5:708–717. doi: 10.1016/j.jcin.2012.05.002.
30. Buchanan GL, Chieffo A, Bernelli C, Montorfano M, Carlino M, Latib A, Figini F, Giannini F, Durante A, Ielasi A, Castelli A, Colombo A. Two-year outcomes following unprotected left main stenting with first vs. new-generation drug-eluting stents: the FINE registry. *EuroIntervention*. 2013;9:809–816. doi: 10.4244/EIJV9I7A134.
31. Bing R, Yong AS, Lowe HC. Percutaneous transcatheter assessment of the left main coronary artery: current status and future directions. *JACC Cardiovasc Interv*. 2015;8:1529–1539. doi: 10.1016/j.jcin.2015.07.017.
32. Park SJ, Kim YH, Park DW, Lee SW, Kim WJ, Suh J, Yun SC, Lee CW, Hong MK, Lee JH, Park SW; MAIN-COMPARE Investigators. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv*. 2009;2:167–177. doi: 10.1161/CIRCINTERVENTIONS.108.799494.
33. de la Torre Hernandez JM, Baz Alonso JA, Gomez Hospital JA, Alfonso Manterola F, Garcia Camarero T, Gimeno de Carlos F, Roura Ferrer G, Recalde AS, Martinez-Luengas IL, Gomez Lara J, Hernandez Hernandez F, Perez-Vizcayno MJ, Cequier Fillat A, Perez de Prado A, Gonzalez-Trevilla AA, Jimenez Navarro MF, Mauri Ferre J, Fernandez Diaz JA, Pinar Bermudez E, Zueco Gil J, Ivus-Tronco-Icp Spanish study. 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;7:244–254. doi: 10.1016/j.jcin.2013.09.014.
34. Park SJ, Ahn JM, Park GM, Cho YR, Lee JY, Kim WJ, Han S, Kang SJ, Park DW, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW. Trends in the outcomes of percutaneous coronary intervention with the routine incorporation of fractional flow reserve in real practice. *Eur Heart J*. 2013;34:3353–3361. doi: 10.1093/eurheartj/eht404.
35. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, Nelis O, Bartunek J, Vanderheyden M, Wyffels E, Barbato E, Heyndrickx GR, Wijns W, De Bruyne B. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation*. 2009;120:1505–1512. doi: 10.1161/CIRCULATIONAHA.109.850073.
36. Courtis J, Rodés-Cabau J, Larose E, Potvin JM, Déry JP, Larochellière RD, Côté M, Cousterousse O, Nguyen CM, Proulx G, Rinfret S, Bertrand OF. Usefulness of coronary fractional flow reserve measurements in guiding clinical decisions in intermediate or equivocal left main coronary stenoses. *Am J Cardiol*. 2009;103:943–949. doi: 10.1016/j.amjcard.2008.11.054.
37. Park SJ, Ahn JM, Kang SJ. Unprotected left main percutaneous coronary intervention: integrated use of fractional flow reserve and intravascular ultrasound. *J Am Heart Assoc*. 2012;1:e004556. doi: 10.1161/JAHA.112.004556.
38. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 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;35:2541–2619. doi: 10.1093/eurheartj/ehu278.
39. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, Naidu SS, Ohman EM, Smith PK. 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. *Circulation*. 2014;130:1749–1767. doi: 10.1161/CIR.0000000000000095.
40. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972. doi: 10.1056/NEJMoa0804626.
41. Zimmermann FM, De Bruyne B, Pijls NH, Desai M, Oldroyd KG, Park SJ, Reardon MJ, Wendler O, Woo J, Yeung AC, Fearon WF. Rationale and design of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 3 Trial: a comparison of fractional flow reserve-guided percutaneous coronary intervention and coronary artery bypass graft surgery in patients with multivessel coronary artery disease. *Am Heart J*. 2015;170:619–626.e2. doi: 10.1016/j.ahj.2015.06.024.
42. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabatè M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet*. 2012;379:1393–1402. doi: 10.1016/S0140-6736(12)60324-9.
43. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50:2173–2195. doi: 10.1016/j.jacc.2007.09.011.
44. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BR, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D,

Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Authors/Task Force Members Chairpersons; Biomarker Subcommittee; ECG Subcommittee; Imaging Subcommittee; Classification Subcommittee; Intervention Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; ESC Committee for Practice Guidelines (CPG); Document Reviewers. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035. doi: 10.1161/CIR.0b013e31826e1058.

45. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol*. 2013;62:1563–1570.
46. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S, 3rd, Bertrand M, Fuster V; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367:2375–2384. doi: 10.1056/NEJMoa1211585.
47. Bravata DM, Gienger AL, McDonald KM, Sundaram V, Perez MV, Varghese R, Kapoor JR, Ardehali R, Owens DK, Hlatky MA. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. *Ann Intern Med*. 2007;147:703–716.
48. Sipahi I, Akay MH, Dagdelen S, Blitz A, Alhan C. Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: meta-analysis of randomized clinical trials of the arterial grafting and stenting era. *JAMA Intern Med*. 2014;174:223–230. doi: 10.1001/jamainternmed.2013.12844.
49. Palmerini T, Biondi-Zoccai G, Reggiani LB, Sangiorgi D, Alessi L, De Servi S, Branzi A, Stone GW. Risk of stroke with coronary artery bypass graft surgery compared with percutaneous coronary intervention. *J Am Coll Cardiol*. 2012;60:798–805. doi: 10.1016/j.jacc.2011.10.912.
50. Mack M, Holmes DR. Randomised trials in left main disease: a NOBLE effort. *Lancet*. 2016;388:2715–2716. doi: 10.1016/S0140-6736(16)32067-0.
51. Taggart DP, Altman DG, Gray AM, Lees B, Gerry S, Benedetto U, Flather M; ART Investigators. Randomized Trial of Bilateral versus Single Internal-Thoracic-Artery Grafts. *N Engl J Med*. 2016;375:2540–2549. doi: 10.1056/NEJMoa1610021.
52. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, Piegas LS, Avezum A, Akar AR, Lanas Zanetti F, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Gao P, Pettit S, Yusuf S; CORONARY Investigators. Five-Year Outcomes after Off-Pump or On-Pump Coronary-Artery Bypass Grafting. *N Engl J Med*. 2016;375:2359–2368. doi: 10.1056/NEJMoa1601564.
53. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR, Jr., Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381:639–650. doi: 10.1016/s0140-6736(13)60108-7.
54. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Ståhle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation*. 2013;128:141–151. doi: 10.1161/CIRCULATIONAHA.113.001803.
55. Nerlekar N, Ha FJ, Verma KP, Bennett MR, Cameron JD, Meredith IT, Brown AJ. percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery stenosis: a meta-analysis of randomized trials. *Circ Cardiovasc Interv*. 2016;9:e004729. doi: 10.1161/CIRCINTERVENTIONS.116.004729.
56. Upadhaya S, Baniya R, Madala S, Subedi SK, Khan J, Velagapudi RK, Bachuwa G. Drug-eluting stent placement versus coronary artery bypass surgery for unprotected left main coronary artery disease: a meta-analysis of randomized controlled trials. *J Card Surg*. 2017;32:70–79. doi: 10.1111/jocs.13090.
57. Park DW, Seung KB, Kim YH, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Yun SC, Gwon HC, Jeong MH, Jang YS, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. 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;56:117–124. doi: 10.1016/j.jacc.2010.04.004.
58. Park DW, Kim YH, Yun SC, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Kim JJ, Choo SJ, Chung CH, Lee JW, Park SW, Park SJ. Long-term outcomes after stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 10-year results of bare-metal stents and 5-year results of drug-eluting stents from the ASAN-MAIN (ASAN Medical Center-Left MAIN Revascularization) Registry. *J Am Coll Cardiol*. 2010;56:1366–1375. doi: 10.1016/j.jacc.2010.03.097.