Editorial

PCI or CABG for severe unprotected left main coronary artery disease: making sense of the NOBLE and EXCEL trials

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In the United States four percent of all patients without a prior history of coronary artery bypass graft (CABG) who undergo coronary angiography have severe unprotected left main coronary artery disease (ULMCAD) (1). Unprotected left main coronary artery disease represents a highly morbid condition with a poor prognosis if not promptly revascularized (2). CABG using the left internal mammary artery was first performed in 1960 and subsequently was shown to be superior to medical therapy at the time (3,4). Thus, CABG became the "gold standard" for which to treat ULMCAD. In the 1980s percutaneous coronary transluminal angioplasty (PCTA) was being used in the management of acute coronary syndromes (ACS) and stable ischemic heart disease (SIHD), however, when compared to CABG, PCTA conferred less symptom improvement and a 10-fold increase in future revascularization (5). To address this short-coming, percutaneous coronary intervention (PCI) with bare metal stent (BMS) placement was developed to reduce the likelihood of target lesion restenosis. Short-term results in low-risk patients were encouraging, however restenosis rates remained ~20–40% over long-term follow-up (6). Drug-eluting stents (DES) effectively addressed the issue of restenosis and the use of PCI to manage ULMCAD began to grow rapidly. In the United States in the early 2000s, the National Cardiovascular Data Registry (NCDR) CathPCI Registry recorded a PCI with DES rate of 17–22% of ULMCAD cases (7). In Asia, the Interventional Research Incorporation Society-Left MAIN Revascularization (IRIS-MAIN) Registry (China, India, Japan, South Korea, Indonesia, Taiwan and Thailand) reported a PCI rate of 46% in the early-to-mid 2000s (8). Subsequently, three randomized controlled trials were performed to evaluate outcomes after PCI with 1st generation DES compared to CABG for ULMCAD: (I) the pre-specified subgroup analysis of the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) Trial (705 patients) showed similar rates of death and major adverse coronary and cerebrovascular events (MACCE) but higher rate of revascularization (26.7% *vs.* 15.5%) with PCI when compared with CABG at 5-year. In the subgroup with low to intermediate SYNTAX scores (≤32) there was a lower rate of death (7.9% *vs.*15.1%) with PCI when compared with CABG (9); (II) the Study of Unprotected Left Main Stenting Versus Bypass Surgery (LE MANS) Trial (105 patients) also showed similar rates of death and MACCE at 1-year between PCI and CABG groups (10); and (III) the Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) (600 patients) showed similar rates of a composite of death, myocardial infarction (MI) or stroke (4.4% with PCI *vs.* 4.7% with CABG) but more revascularization with PCI (9.0% *vs.* 4.2%) over five years of follow-up (8). The evidence from these three trials led to the American College of Cardiology Foundation/American Heart Association (ACCF/AHA)

2012 Guidelines for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease recommending CABG with a class of recommendation (COR) I (level of evidence B) and recommending PCI with a COR IIa (level of evidence B) if the patient has high surgical-risk and non-complex anatomy (SYNTAX <22) (11). These recommendations were not changed in the 2014 update (12). The European Society of Cardiology/European Society of Cardiothoracic Surgeons (ESC/ESCTS) 2014 Guidelines on Myocardial Revascularization similarly recommend CABG with a COR I (level of evidence B) for ULMCAD, but differed in that they recommended PCI with a COR I (level of evidence B) for low complex anatomy (SYNTAX ≤22), a COR IIa for intermediately complex anatomy (SYNTAX 23–32) and COR III for highly complex anatomy (SYNTAX >32).

However, since the aforementioned trials, PCI technology and techniques have advanced considerably. Second generation DES, with ultra-thin cobalt-chromium or platinum-chromium struts, newer mTOR inhibitor chemotherapeutic eluents and durable or bio-resorbable polymers, have dramatically reduced the risk of restenosis and stent thrombosis (13). Similarly, techniques for PCI of ULMCAD have advanced and certain ULMCAD anatomy has been identified to confer worse outcomes with PCI, distal/bifurcation disease in particular (14). Intravascular ultrasound (IVUS) imaging guidance has become standard practice with improved characterization of the stenosis and plaque distribution, as well as better assessment of stent deployment (15,16). With these advances, recent data from the New York State registries showed that in patients with multivessel disease (without left main disease) who received Everolimus-eluting stents (EES) had similar survival compared to CABG (17). PRECOMBAT-2 retrospectively assessed 334 consecutive patients who received EES or Sirolimus-eluting stents (SES) versus CABG and found similar rates of death and MACCE but more revascularization with PCI in patients with ULMCAD (18). Up to this point, no prospective, randomized data existed comparing 2nd generation DES to CABG for revascularization of ULMCAD. Therefore, the questions remains if PCI with 2nd generation DES provide comparable results to CABG in patients with ULMCAD. Two recently published trials attempt to address that question.

The Nordic-Baltic-British left main revascularization study (NOBLE) is a prospective, randomized, non-inferiority trial designed to compare PCI with CABG for the revascularization of severe ULMCAD in SIHD, unstable angina, or non-ST elevation myocardial infarction (NSTEMI). To be eligible, patients must have had a visual lesion severity of ≥50% or a fractional flow reserve (FFR) ≤0.80 in the left main coronary artery and no more than three additional non-complex lesions. 1,201 patients from 36 centers were enrolled from December 9, 2008 to January 21, 2015. They were randomly assigned to either CABG with arterial graft or PCI with a 2nd generation DES which was primarily the Biolimus-eluting DES (BIOMATRIX™, Biosensors International, Morges, Switzerland); a 120-micron stainless steel stent with a biodegradable polymer. However, 11% of patients in the PCI group received a 1st generation DES. The primary endpoint was a composite of all-cause mortality, spontaneous MI, stroke and repeat revascularization at Kaplan-Meier estimate at 5-year. The primary endpoint occurred in 28% of patients in the PCI group and 18% of patients in the CABG group [HR =1.51 (95% CI, 1.13–2.00), P=0.01] crossing the threshold for non-inferiority and was statistically significant for superiority of CABG over PCI (P=0.004). All-cause mortality and stroke was similar between the two groups, but there were more spontaneous MI [HR =2.87 (95% CI, 1.40–5.89), P=0.004], and more repeat revascularization in the PCI group [HR =1.50 (95% CI, 1.04–2.17), P=0.03], however target lesion repeat revascularizations were similar (*Table 1*). The authors concluded that "CABG might provide a better clinical outcome for treatment of left main coronary artery disease than PCI".

The EXCEL trial is a prospective randomized, non-inferiority trial designed to compare PCI with CABG for the revascularization of severe ULMCAD in SIHD and ACS, including ST-segment elevation MI (STEMI). To be included patients must have had a visual lesion severity of ≤70% or, if 50–70%, an FFR ≤0.80 in the left main coronary artery, been deemed eligible for either method of revascularization by a "heart team", and a SYNTAX score <32. A total of 1,905 patients from 131 centers were enrolled from September 16, 2010 to June 3, 2014. They were randomly assigned to either CABG with arterial graft, or PCI with the 2nd generation DES EES (XIENCE™, Abbott Vascular, Santa Clara, CA, USA), an 81-micron cobalt-chromium stent with a durable polymer. The primary endpoint was a composite of all-cause mortality, any MI and stroke. The primary endpoint occurred in 15.4% of patients in the PCI group and 14.1% of patients in the CABG group [HR =1.00 (95% CI, 0.79–1.26), P=0.98] meeting statistical criteria for non-inferiority of PCI to CABG. All-cause

Table 1 NOBLE and EXCEL trials: similarities and differences

Variables	NOBLE trial	EXCEL trial
Trial design		
Patient characteristics	STEMI within 24 h excluded	All ACS eligible
Anatomic characteristics	ULMCAD stenosis >50% or FFR<0.80; no more than 3 additional lesion or complex addition lesion	ULMCAD stenosis >70% or if 50–70% then FFR<0.80; SYNTAX <32
Primary endpoint	Death, spontaneous MI, stroke or revascularization	Death, any MI or stroke
Geographic region	100% Europe	56% Europe, 40% North America, 4% Other*
Sample size	1,201	1,905
Median follow-up time	3.1 years	3.0 years
Study population		
SYNTAX score	22.5±7.5	20.6±6.2
ACS	18%	15% (1.4% STEMI)
LVEF	60% (IQR 55–65%)	57%±10%
Diabetes	PCI group: 15%; CABG group: 15%	PCI group: 32.2%; CABG group: 28.0%
Procedural characteristics		
Stent used	89% biolimus-eluting stent (BIOMATRIX™), 11% 1st Gen DES	100% everolimus-eluting stent (XIENCE™)
Distal/bifurcation disease	81%	81%
IVUS guidance	Pre-stent evaluation: 47%; post-stent evaluation: 77%	IVUS guidance: 77%
2-stents used	37%	NR
2-stent technique	Culotte: 24%; crush: 4%; other: 9%	NR
LIMA to LAD	96%	98.8%
Only arterial grafts used	14.3%	24.8%
Results: PCI *vs.* CABG		
Primary endpoint	Favors CABG	No difference
All-cause-mortality	No difference	No difference
Cardiac mortality	No difference	No difference
Total MI	NR	No difference
Spontaneous MI	Favors CABG	No difference
Stroke	No difference	No difference
Total revascularization	Favors CABG	Favors CABG
Target-lesion revascularization	No difference	No difference
LMCA revascularization	No difference	NR
Stent thrombosis	2%†, 0.8% (BIOMATRIX™ DES only)†	0.7%‡

*, Australia, South America, South Korea; †, based on Kaplan-Meier 5-year estimates; ‡, based on Kaplan-Meier 3-year estimates. ACS, acute coronary syndrome; DES, drug-eluting stent; IVUS, intra-vascular ultrasound; HR, hazard ratio; LVEF, left ventricular ejection fraction; NR, not reported; NS, not significant; STEMI, ST-segment elevation myocardial infarction; ULMCAD, unprotected left main coronary artery disease.

mortality, cardiac mortality, total MI, spontaneous MI and stroke were similar between the PCI and CABG groups (*Table 1*). There were more total repeat revascularizations in the PCI group [HR =1.72 (95% CI, 1.27–2.33), P<0.001], however target lesion repeat revascularizations were similar. The authors concluded that "PCI with EES was non-inferior to CABG with respect to the composite endpoint of death, stroke or myocardial infarction at 3 years". It is worth noting, however, that some have suggested that the non-inferior margin used in EXCEL was too liberal (4.2%) and may have biased the results towards non-inferiority (19).

When interpreting the results of EXCEL and NOBLE, the first thing one must keep mind is that the benefit of CABG is often seen after extended follow-up (20). Both studies had a median follow-up duration of 3.1 years, which is relatively short, hence longer term follow-up is needed before making any concrete conclusions. EXCEL and NOBLE had a number of similarities, and a few differences (*Table 1*). EXCEL recruited 704 more patients then NOBLE. The mean SYNTAX score of EXCEL was 20.6±6.2 versus NOBLE which was 22.5 (IQR 55–65%), but most notably they had the exact same rates of distal bifurcation disease, 81%. Procedural data was not reported in EXCEL, so the details of the bifurcation PCI technique are unknown, but IVUS guidance was used in 77% of cases in EXCEL compared to 47% pre-stent and 77% post-stent in NOBLE. Both NOBLE and EXCEL did not find any significant difference in all-cause-mortality or cardiac-death between PCI and CABG. However, there was more spontaneous MI in the PCI group (6%) in NOBLE, which contributed to its composite endpoint. In EXCEL there was similar rates of spontaneous MI in the PCI group (4.3%). This difference in rates of spontaneous MI in the PCI groups between the two studies may be a reflection of the different stents that were used between the two trials. In Noble, 49 patients (11%) who underwent PCI received a 1st generation DES. The 2nd generation DES biolimus-eluting stent (BES) was not introduced as the "stent of choice" until well into enrollment. Moreover, subsequent meta-analysis has shown that the BES has an inferior safety profile compared to the EES (21). The difference in stents used could also explain the higher definite stent thrombosis rate. In NOBLE, there was a 2% definite stent thrombosis rate on 5-year Kaplan Meier estimates (0.8% for recipients of the BES) compared to EXCEL which had a 0.7% rate of stent thrombosis on 3-year Kaplan-Meier estimates (22). In NOBLE, the higher rate of spontaneous MI and revascularization drove the primary composite endpoint in favor of CABG leading the authors to conclude that CABG was superior to PCI for ULMCAD revascularization. Where in EXCEL spontaneous MI rates were similar between treatment arms, and revascularization was not included in the primary composite endpoint, leading them to conclude that PCI and CABG conferred a similar benefit.

The take-home message from the NOBLE and EXCEL trials is that PCI and CABG confer a similar survival benefit in revascularization of ULMCAD over intermediate-term follow-up. Repeat revascularization is more likely with PCI compared to CABG, and there may be an increased risk of spontaneous MI with PCI when using non-EES DES. Another important observation from these studies is the high rate of bifurcation disease in the ULMCAD population. This observation reinforces the need for having an experienced heart team, familiar with current best practices and techniques, managing these patients to achieve optimal outcomes. Longer-term follow-up data from both trials will be reported in due time and will provide insights into the durability of the results for both PCI and CABG. The decision between PCI and CABG for ULMCAD should be based on weighing the benefits and risks of PCI versus CABG and taking patient preference into consideration.

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Footnote

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References

1. Weintraub WS, Stein B, Kosinski A, et al. Outcome of coronary bypass surgery versus coronary angioplasty in diabetic patients with multivessel coronary artery disease. J Am Coll Cardiol 1998;31:10-9.
2. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Long-term CASS experience. Circulation 1995;91:2325-34.

3. Goetz RH, Rohman M, Haller JD, et al. Internal mammary-coronary artery anastomosis. A nonsuture method employing tantalum rings. J Thorac Cardiovasc Surg 1961;41:378-86.
4. Takaro T, Hultgren HN, Lipton MJ, et al. The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. Circulation 1976;54:III107-17.
5. King SB 3rd, Lembo NJ, Weintraub WS, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). N Engl J Med 1994;331:1044-50.
6. Black A, Cortina R, Bossi I, et al. Unprotected left main coronary artery stenting: correlates of midterm survival and impact of patient selection. J Am Coll Cardiol 2001;37:832-8.
7. Huang HW, Brent BN, Shaw RE. Trends in percutaneous versus surgical revascularization of unprotected left main coronary stenosis in the drug-eluting stent era: a report from the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). Catheter Cardiovasc Interv 2006;68:867-72.
8. Lee PH, Ahn JM, Chang M, et al. Left Main Coronary Artery Disease: Secular Trends in Patient Characteristics, Treatments, and Outcomes. J Am Coll Cardiol 2016;68:1233-46.
9. 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.
10. 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.
11. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44-e164.
12. 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.
13. Bangalore S, Toklu B, Amoroso N, et al. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. BMJ 2013;347:f6625.
14. Tiroch K, Mehilli J, Byrne RA, et al. Impact of coronary anatomy and stenting technique on long-term outcome after drug-eluting stent implantation for unprotected left main coronary artery disease. JACC Cardiovasc Interv 2014;7:29-36.
15. Oviedo C, Maehara A, Mintz GS, et al. Intravascular ultrasound classification of plaque distribution in left main coronary artery bifurcations: where is the plaque really located? Circ Cardiovasc Interv 2010;3:105-12.
16. Puri R, Kapadia SR, Nicholls SJ, et al. Optimizing outcomes during left main percutaneous coronary intervention with intravascular ultrasound and fractional flow reserve: the current state of evidence. JACC Cardiovasc Interv 2012;5:697-707.
17. Bangalore S, Guo Y, Samadashvili Z, et al. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. N Engl J Med 2015;372:1213-22.
18. Kim YH, Park DW, Ahn JM, et al. 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;5:708-17.
19. BelleyCote EP, Lamy AR, Whitlock RP. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Disease. N Engl J Med 2017;376:1087-8.
20. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. N Engl J Med 2016;374:1511-20.
21. Kang SH, Chae IH, Park JJ, et al. Stent Thrombosis

With Drug-Eluting Stents and Bioresorbable Scaffolds: Evidence From a Network Meta-Analysis of 147 Trials. JACC Cardiovasc Interv 2016;9:1203-12.
22. Christiansen EH, Makikallio T, Hildick-Smith D, Thuesen L, Holm NR, investigators Ns. Stents versus bypass surgery for left main stem stenosis - Authors' reply. Lancet 2017;389:1609.

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