"You don't need a weather man to know which way the wind blows": understanding differences and applications in clinical practice of randomized controlled trials on unprotected left main

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Stenosis of unprotected left main coronary artery (ULMCA) is reported in about 6% of patients undergoing coronary angiography with a negative prognostic impact (1).

Revascularization strategies have always been a hot topic for cardiologist and cardiac surgeons due to the technical difficulties and to contrasting clinical evidence. In 1975 Drs. Cohen and Gorlin first, demonstrated an improvement in long-term mortality for patients treated with coronary artery bypass grafting (CABG) compared to medical therapy (2).

Introduction of percutaneous coronary intervention (PCI) has offered more choices for these patients. First attempts with PCI with bare metal stents (BMSs) showed an overall high mortality and revascularization rates, with a downgrading in European and American guidelines to class III for percutaneous management of these patients, reserving PCI only for patients disqualified from all other possible methods of treatment.

Introduction of drug eluting stents (DES) has rapidly changed this scenario. The first "landmark" trial comparing PCI with DES to CABG for LMCAD (and multivessel diseases) was the SYNTAX trial (3). This was a multicenter, randomized, prospective trial conduced in 2009 and designed as a "non-inferiority" analysis between DES (first generation stent, Taxus Express paclitaxel-eluting stents, Boston Scientific) and CABG for a composite clinical end point of major adverse cardiac and cerebrovascular events throughout a 12-month period after randomization. A superficial analysis of this trial's results could lead any reader to deduce that CABG is the best option for patients with LMCAD, since the non-inferiority outcome was not met. However, this result was mainly driven by repeated revascularization, while the overall and the combined end point of death from any cause, stroke, or myocardial infarction was not statistically different. From these data the authors derived a score that tried to stratify the patients according the anatomical characteristics of the vessels and the functional risk of occlusion for any segment of the coronary-artery bed (SYNTAX score) identifying who could benefit the most from an interventional or surgical approach. This probably determined, despite the main result of the SINTAX, the opening from American guidelines to PCI in LMCAD and the progressive upgrading recommendation from class III to IIA in patients with an intermediate risk score (SYNTAX score 23–32) and class I, level of evidence B, for patients with a low risk score (SINTAX score <23). The main results were confirmed at 5 years of follow-up (4). After 6 years, many other smaller and non-randomized trials (5-7) have been carried out and their results substantially agreed with SYNTAX findings. Similarly longer follow up to 10 years confirmed the previous finding (8,9).

Recently two important papers have been published in this field: the Danish study "Percutaneous coronary angioplasty versus coronary artery bypass grafting in

treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial" (NOBLE trial) (10) and the "Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease" (EXCEL trial) (11).

Even if these two trials have a similar intention and both have been prompted from improvements in PCI techniques and technologies, above all the spreading of the second generation DES [everolimus eluting stents (EES), Abbott Vascular™] in EXCEL and biolimus eluting stents (BES) in NOBLE (Biosensors International™) they are different for many reasons (*Table 1*).

The main difference is in the primary endpoint of the two trials. In NOBLE the primary endpoint was a composite of death, stroke, non-index treatment-related myocardial infaction (MI) and new revascularization (MACCE) at 3 years, whereas in EXCEL the primary endpoint was a composite of death, MI and stroke at 3 years. This obviously implicated a different sample size required (1,200 pts *vs.* 1,905 pts respectively). Another relevant difference involved inclusion and exclusion criteria: the EXCEL trial included patients with a SINTAX score less than 33, while NOBLE trial excluded patients in witch "CABG was clearly the better treatment option", referring to LM stenosis with more than three additional lesions or more complex ones, not clearly stratified by SINTAX score calculation, leaving some doubt in the comparability of the two population. Further, the NOBLE trial adopted as significant an ULMCA with a visually assessed diameter stenosis (DS) >50% or fractional flow reserve (FFR) <0.80, while the EXCEL trial reported significant ULMCA as one of the following: DS ≥70% (visually estimated) or DS ≥50% but <70% [requiring non-invasive or invasive (FFR ≤0.80) evidence of ischaemia or intravascular ultrasound (IVUS) minimal lumen area (MLA) ≤6.0 mm^2].

As stated by the recent Noble Prize Bob Dylan, all these differences in inclusion criteria and definition lead, not unexpectedly, to different results, even without a "weather man" to explain these. Actually the EXCEL trial showed that PCI is non-inferior to CABG at 3 years suggesting that PCI with everolimus-eluting stents is an acceptable or perhaps the preferred alternative to CABG in selected patients with left main coronary artery disease who are candidates for either procedure. On the opposite, the NOBLE authors state that Kaplan-Meier estimates of MACCE after 5 years are clearly favorable to CABG, since the non-inferiority limit was exceed in the statistical analysis.

These contrasting results from trials that were supposed to definitively address the optimal medical choice in LMCAD generated a lot of disappointment among cardiac surgeons and interventional cardiologists.

But, probably, these findings are not so different as they appear. The first reason clearly concerns the different outcome they looked at. The EXCEL trial did not consider, in its main combined endpoint, the rate of revascularization instead of the NOBLE study, as previously stated. The sub-analysis of the different events occurring during the follow up, and contributing to the final count of MACCE, among the two randomized population of the NOBLE shows that a statistically meaning difference exists only in the rate of non-procedural myocardial infarction (HR 2.88) and in the number of total revascularization needed (HR 1.50), while interestingly target revascularization on LMCAD were similar (10% *vs.* 9%). This finding confirms a good outcome of LM PCI, while the repeated revascularizations were probably due to CAD progression in other sites. On the other hand, EXCEL authors, in the valuation of secondary endpoints, state that the 3-year rate of revascularization was five percentage points higher with PCI with everolimus-eluting stents than with CABG.

It is also remarkable that the main NOBLE endpoint included only non-procedural myocardial infarction (thus meaning that AMI happening during the first 30 days after the index procedure were not counted). This data has to be carefully considered. Even if the EXCEL had a different and less sensible definition of AMI (CK-MB 10 times the greater limit of normal) the rate of the composite end-point events (thus including myocardial infarction) within 30 days after PCI or CABG was lower in the PCI group than in the CABG group, whereas fewer primary end-point events occurred in the CABG group than in the PCI group between 30 days and 3 years after the procedure.

Finally, it is necessary to underline that in NOBLE trial has a longer follow-up (5 years) compared with the EXCEL trial (3 years). This must be pointed out since a recent meta-analysis data of CABG versus medical therapy, showed that the real benefit of an invasive strategy was evident at the 5- to 10-year phase, despite PCI shows an acceptable outcome in long term follow-up (9).

By our point of view, as shown by the EXCEL trial, both strategies are suitable being the hard end-point similar, probably further longer-term data from the trials are needed. Anyway, considering the difficulties in enrolling patients in these types of trials and their notable costs we suppose that no other major trials will be carried out

Table 1 Comparison between NOBLE and EXCEL trials

Variable	EXCEL	NOBLE
Main inclusion criteria	(I) Patients with silent ischemia, stable angina, unstable angina or recent MI (if recent MI, CK-MB must have returned to normal); (II) significant ULMCA disease or left main equivalent disease. Significant lesion defined as: DS ≥70% (visually estimated) or DS ≥50% but <70% [requiring non-invasive or invasive (FFR ≤0.80) evidence of ischemia or IVUS minimal lumen area (MLA) ≤6.0 mm^2]; (III) clinical and anatomic eligibility for both PCI and CABG as agreed to by the local Heart Team (SYNTAX score <33); excluded visually estimated left main reference vessel diameter <2.25 or >4.25 mm (post-dilatation up to 4.5 mm is allowed)	(I) Stable, unstable angina pectoris or ACS (ST-elevation infarction within 24 hours excluded); (II) significant ULMCA with no more than three additional non-complex PCI lesions. Significant lesion defined as: a visually assessed DS >50% or FFR <0.80; (III) patient eligible to be treated by CABG and by PCI
Stent type	EES (everolimus eluting stents)	BES (biolimus eluting stents)
Sample size (No. of patients)	1,905	1,200
Follow up (years)	3	5
Primary outcome (definition)	Death, MI (considered all episodes after index events) or stroke	Death, stroke, non-procedural MI (occurred after first 30 days from index event) or new revascularization
Main result	PCI not inferior to CABG: 15.4% (PCI) *vs.* 14.7% (CABG), P=0.02 for non-inferiority; HR 1.00 (95% CI, 0.79–1.26); P=0.98 for superiority	CABG better than PCI: 29% (PCI) *vs.* 19% (CABG), HR 1.48 (95% CI, 1.11–1.96; P=0.01); CABG was significantly better than PCI (P=0.0066 for superiority)
Main sub-analysis or secondary outcomes results	(I) MI 8% (PCI) *vs.* 8.3% (CABG), HR 0.93 (95% CI, 0.67–1.28, P=0.64); (II) revascularization 12.6% (PCI) *vs.* 7.5% (CABG), HR 1.72 (95% CI, 1.27–2.33, P<0.001); (III) ischemia driven TVR 10.9% (PCI) *vs.* 7.2% (CABG) HR 1.55 (95% CI, 1.13–2.13; P=0.006)	(I) Non-procedural myocardial infarction 7% (PCI) *vs.* 2% (CABG), HR 2.88 (95% CI, 2.40–5.90; P=0.004); (II) revascularization 16% (PCI) *vs.* 10% (CABG), HR 1.50 (95% CI, 1.04–2.17; P=0.032); (III) TVR 10% (PCI) *vs.* 9% (CABG), HR 1.23 (95% CI, 0.78–1.94; P=0.37)

MI, myocardial infaction; ACS, acute coronary syndrome; ULMCA, unprotected left main coronary artery; DS, diameter stenosis; FFR, fractional flow reserve; IVUS, intravascular ultrasound; TVR, target vessel revascularization; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

in this field in the near future. From a scientific point of view, this means that large meta-analysis including all best-quality trials are highly required and that they could help to overcome real or apparent divergences.

From a clinical point of view, it remains mandatory to remember that where the evidence based medicine seems to leave us at the mercy of our personal experience, it is time to get back to the patient based medicine. This means that the best choice for LMCAD cannot leave aside single patient characteristics, comorbidities and personal preferences. This goal is only achievable trough a multidisciplinary approach. As interventional cardiologist, we should never forget that CABG could be the best option treatment for patients with high SYNTAX score or for example very calcified chronic total occlusion or multiple vessels disease. On the other hand cardiac surgeons should be able to consider PCI as the first alternative in patients with higher EuroSCORE, in aged patients with low expectancy of life, with prior strokes, sever comorbidities or in whom distal coronary bed is unlikely to receive optimally a graft.

The left main coronary is not a battlefield between cardiac surgeons and interventional cardiologist, and the

best choice for our patients is not an option, but should derive from an accurate risk stratification.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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