LM Interventions Up to date

EXCEL AND NOBLE TRIALS

HOW TO READ THE DIFFERENCE?

Mohamd Abd Elghany

BACKGROUND

- Left main coronary artery disease is associated with high morbidity and mortality owing to the large amount of myocardium at risk.
- Prevalence of significant ULMCA disease

  4-6% of all patients who undergo coronary angiography

  24% of patients with acute coronary syndrome

Recommendation for the type of revascularization (CABG or PCI) in patients with SCAD with suitable coronary anatomy for both procedures and low predicted surgical mortality

Recommendations according to extent of CAD	CABG		PCI		
	Class[a]	Level[b]	Class[a]	Level[b]	Ref[c]
One or two-vessel disease without proximal LAD stenosis.	IIb	C	I	C	
One-vessel disease with proximal LAD stenosis.	I	A	I	A	107,108,160, 161,178,179
Two-vessel disease with proximal LAD stenosis.	I	B	I	C	108,135,137
Left main disease with a SYNTAX score ≤ 22.	I	B	I	B	17,134,170
Left main disease with a SYNTAX score 23–32.	I	B	IIa	B	17
Left main disease with a SYNTAX score >32.	I	B	III	B	17
Three-vessel disease with a SYNTAX score ≤ 22.	I	A	I	B	17,157,175,176
Three-vessel disease with a SYNTAX score 23–32.	I	A	III	B	17,157,175,176
Three-vessel disease with a SYNTAX score >32.	I	A	III	B	17,157,175,176

2014 ESC/EACTS Guidelines on myocardial revascularization

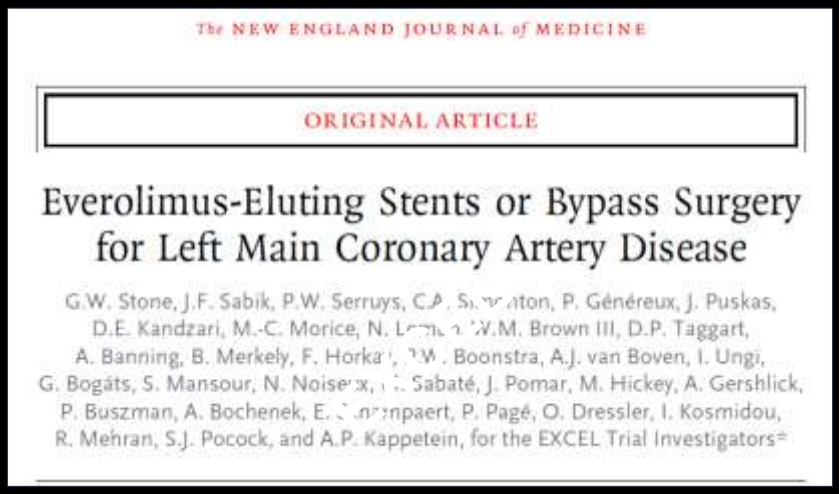
WHY A NEW TRIAL??

- There are numerous studies (PCI versus CABAG)
- Subset analysis from the SYNTAX trial suggested that DES may be an acceptable option for pts with LMCAD and low or moderate CAD complexity
- PRECOMBAT and some other trials were not adequately powered.
- Meta-analytic combinations of previous studies --→ PCI has similar five-year mortality and myocardial infarction, with a lower incidence of stroke and increased risk of repeat revascularisation when compared to CABG
- Moreover, new drug-eluting stents have a better safety and efficacy profile than do the first-generation stents used in earlier trials.

Surgical techniques and outcomes have also continued to improveoronary artery bypass graft surgery versus percutaneous coronary intervention with first-generation drug-eluting stents: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv. 2014

Two new dedicated randomised trials
comparing CABG and PCI

EXCEL and NOBLE



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease

G.W. Stone, J.F. Sabik, P.W. Serruys, C.A. S[illegible]ton, P. Généreux, J. Puskas, D.E. Kandzari, M.-C. Morice, N. L[illegible] W.M. Brown III, D.P. Taggart, A. Banning, B. Merkely, F. Horka[illegible], [illegible]W. Boonstra, A.J. van Boven, I. Ungi, G. Bogáts, S. Mansour, N. Noiseux, [illegible]. Sabaté, J. Pomar, M. Hickey, A. Gershlick, P. Buszman, A. Bochenek, E. [illegible]npaert, P. Pagé, O. Dressler, I. Kosmidou, R. Mehran, S.J. Pocock, and A.P. Kappetein, for the EXCEL Trial Investigators*

This article was published on October 31, 2016, at NEJM.org

Trial design

EXCEL was an

- International,
- Open-label,
- Multicenter (126 sites in 17 countries)
- Randomized Trial

- Designed to establish the safety and efficacy of the everolimus-eluting stent (XIENCE PRIME™ or XIENCE V® or XIENCE Xpedition™ or XIENCE PRO™; Abbott Vascular, Santa Clara, CA, USA) in patients with significant ULMCA disease.

Inclusion criteria

1a. Unprotected LMCAD with angiographic diameter stenosis ≥70% (visually estimated), or with angiographic diameter stenosis ***≥50% but <70%*** with one or more of the following present:

a. Non-invasive evidence of ischemia referable to a hemodynamically significant left main lesion, and/or

b. IVUS MLA ≤6.0 mm**2, and/or**

c. FFR ≤0.80 OR

1b. LM equivalent disease: Left main distal bifurcation Medina 0,1,1 disease, in the absence of significant angiographic stenosis in the left main coronary artery, may also be randomized if either of the following conditions are present:

i. Both the ostial LAD and ostial LCX stenoses are ≥70% stenotic by visual estimation, or

ii. If one or both of the ostial LAD and ostial LCX stenoses are ≥50% - <70% stenotic by visual estimation, then this lesion(s) is demonstrated to be significant either by

i. non-invasive evidence of ischemia in its myocardial distribution; and/or

ii. FFR ≤0.80; and/or

iii. IVUS MLA ≤4.0 mm2 (FFR is preferred).

Objectives and End Points

- **PRIMARY ENDPOINT OUTCOME**

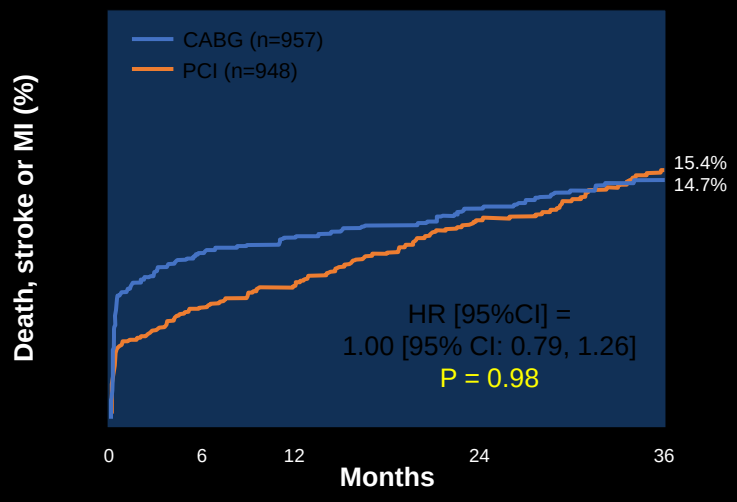
Composite rate of death from any cause, stroke, or myocardial infarction at 3 years

- **SECONDARY OUTCOMES**

1)Composite rate of death from any cause, stroke, or myocardial infarction at 30 days

2) Death, stroke , MI or Ischemia driven revacularization at 3 years

Primary Endpoint
Death, Stroke or MI at 3 Years



Primary and Secondary Clinical End Points

Clinical end point at 3 yars	PCI (n=948), %	CABG (n=957), %	Hazard ratio (95% CI)	*P*
CV death	4.4	3.7	1.18 (0.74–1.87)	0.48
Non-CV death	3.9	2.3	1.60 (0.91–2.80)	0.10
Stroke	2.3	2.9	0.77 (0.43–1.37)	0.37
MI	8.0	8.3	0.93 (0.67–1.28)	0.64
Periprocedural MI	3.8	6.0	0.63 (0.42–0.96)	0.03
Ischemia-driven revascularization	12.6	7.5	1.72 (1.27–2.33)	<.001

EXCEL Conclusions

- Treatment of patients with LMCAD and low or intermediate SYNTAX scores with EES resulted in similar rates of the primary endpoint of death, stroke or MI at 3 years, with fewer adverse events within 30 days compared to CABG
- PCI may thus be considered an acceptable or even preferred revascularization modality for selected patients with LMCAD, a decision which should be made after heart team discussion, taking into account each patient's individual circumstances and preferences

THE LANCET

Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial

*Timo Mäkikallio, Niels R Holm, Mitchell Lindsay, Mark S Spence, [illegible], Ian B A Menown, Thor Trovik, Markku Eskola, Hannu Romppanen, Thomas Kellerth, Jan Ravkilde, Lisette O Jensen, Gintaras Kalinauskas, Eckard B A Linder, Markku Pentikainen, Anders Hervold, Adrian Banning, Azfar Zaman, James Cotton, Erlend Eriksen, Sulev Margus, Jenni T Sørensen, Per H Nielsen, Matti Niemelä, Kari Kervinen, Jens F Lassen, Michael Maeng, Keith Oldroyd, Geoff Berg, Simon J Walsh, Colm G Han[illegible]dulis Kumsars, Peteris Stradins, Terje K Steigen, Ole Fröbert, Alastair N J Graham, Petter C Endresen, Matthias Corbascio, Olli Kajander, Uday Trivedi, Juha Hartikainen, Vesa Anttila, David Hildick-Smith, Leif Thuesen, Evald H Christiansen, for the NOBLE study investigators**

Published online October 31, 2016

The NOBLE trial is

- an international,
- prospective, unblinded, randomised multicentre trial
- Randomised 1,200 patients in 36 centers.
- The biolimus-eluting stent BioMatrix™ (Biosensors, Morges, Switzerland) is the recommended study stent but other CE-marked DES may be used at operators' discretion (88% was biolimus)

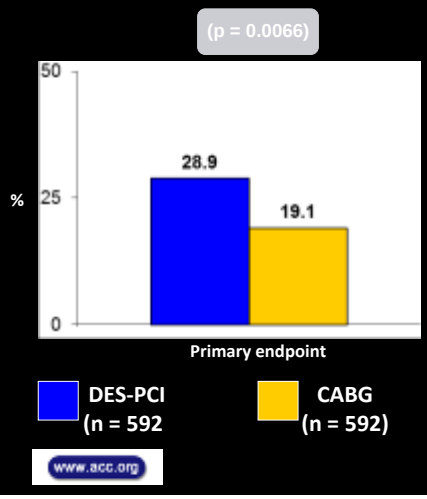
Primary endpoint

- **A composite of major adverse cardiac and cerebrovascular events (MACCE)**
  - **Death from any cause**
  - **Non-procedural myocardial infarction**
  - **Repeat revascularization**
  - **Stroke**

Secondary endpoints

- The individual components of the primary endpoint
- Definite stent thrombosis
- Symptomatic graft occlusion
- Procedural myocardial infarction (post hoc)
- Repeat revascularization
  - Target lesion
  - Left main coronary artery target lesion
  - De novo lesion

NOBLE



Results

- Primary endpoint: Death/MI/stroke/repeat revasc: PCI vs. CABG: 28.9% vs. 19.1%, p = 0.0066
- Death: 11.6% vs. 9.5%, p = 0.77;
- MI: 6.9% vs. 1.9%, p = 0.004;
- stroke: 4.9% vs. 1.7%, p = 0.07;
- repeat revasc: 16.2% vs. 10.4%, p = 0.03; de novo lesion revasc: 6% vs. 3%, p = 0.018
- Stent thrombosis/graft occlusion: 3% vs. 4%, p = 0.22

Mäkikallio T, et al. Lancet 2016

NOBLE Conclusions

- PCI did not meet non-inferiority for the primary endpoint of **5-year** MACCE compared to CABG

- **CABG was superior to PC I**

- First 30 days: The hazard was highest with CABG with better outcomes with PCI

- between 30 days and 5 years : outcomes were inferior with PCI compared with CABG

- PCI resulted in higher rates of non-procedural myocardial infarctions
- Repeat revascularization was higher after PCI, primarily due to de novo lesions and non LMCA target lesion revascularization
- All-cause mortality was similar for PCI and CABG

Question

Is PCI with DES should be preferred as an alternative to CABG surgery in patients LM disease

conflicting data from the two late-breaking clinical trials

Differences

The 1st difference between EXCEL and NOBLE is

(**Assessment of ULMCA significance**)

- ***The NOBLE trial*** : visually assessed diameter stenosis >50% or fractional flow reserve (FFR) <0.80.
- ***The EXCEL trial*** : -defines 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 IVUS minimal lumen area [MLA] ≤6.0 mm2).

-EXCEL trial has enrolled patients with LM equivalent disease (Medina classification 0,1,1) with both the ostial LAD and ostial LCX stenoses having ≥70% DS

Differences

The second difference (criteria of inclusion)

- ***EXCEL trial*** : enrolled patients with ULMCA disease up to intermediate anatomical complexity defined by a SYNTAX score <33
- ***NOBLE trial*** : enrolled patients with ostium, mid-shaft and/or bifurcation and with no more than three additional non-complex PCI lesions

Non-complex lesions in the NOBLE trial were defined as length <25 mm, non-chronic total occlusion, non-two-stent bifurcation, non-calcified and non-tortuous coronary lesions.

Differences

The 3rd difference. (Study device)

- ***EXCEL :*** the workhorse stent was the everolimus-eluting stent (EES) (XIENCE)……. more contemporary stent

- ***NOBLE*** : the workhorse drug-eluting stent is a biolimus-eluting stent (BES) (BioMatrix) with bioabsorbable polymer

SES: previous randomized comparisons of everolimus- versus paclitaxel-eluting stents were designed and powered for a combination of angiographic, ischemic and safety outcomes, and have consistently shown the EES to be associated with more favorable outcomes compared to paclitaxel-eluting stents

BES: high radial strength and expansion capacity- excellent results in comparison with first as well as second-generation DES

Differences

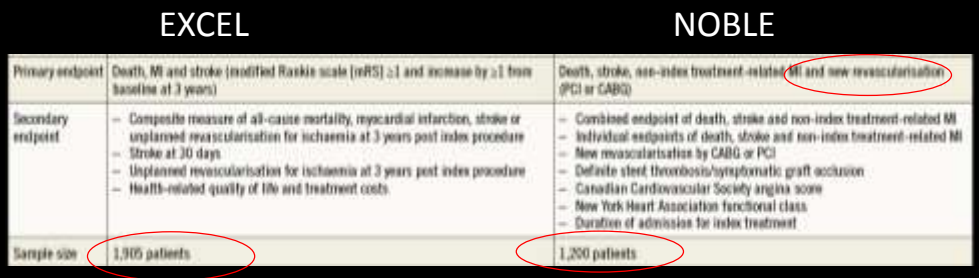
The 4th difference. (IVUS)

- a lower rate of ultrasound validation of stent deployment in NOBLE

Differences

The 5th difference. (Primary endpoints)

Repeat revascularization was one of the end points in NOBLE (it's not equivalent to death or MI or stroke)



	EXCEL	NOBLE
Primary endpoint	Death, MI and stroke (modified Rankin scale (mRS) ≥1 and increase by ≥1 from baseline at 3 years)	Death, stroke, non-index treatment-related MI and new revascularisation (PCI or CABG)
Secondary endpoint	– Composite measure of all-cause mortality, myocardial infarction, stroke or unplanned revascularisation for ischaemia at 3 years post index procedure – Stroke at 30 days – Unplanned revascularisation for ischaemia at 3 years post index procedure – Health-related quality of life and treatment costs	– Combined endpoint of death, stroke and non-index treatment-related MI – Individual endpoints of death, stroke and non-index treatment-related MI – New revascularisation by CABG or PCI – Definite stent thrombosis/symptomatic graft occlusion – Canadian Cardiovascular Society angina score – New York Heart Association functional class – Duration of admission for index treatment
Sample size	1,905 patients	1,200 patients

Results : EXCEL versus NOBLE

- **In EXCEL**

- At 30 days, there was a significant 39% reduction in the composite of death, stroke, or MI among the PCI patients driven largely by fewer large MIs in the PCI group.

-However, that a post hoc landmark analysis revealed "**a catch-up**" between 30 days and 3 years in the PCI group vs the CABG group, with increases in primary-end-point events (11.5% vs 7.9%; *P*=0.02) and more ischemia-driven revascularization

"once past the 30-day -→noninferiority end point is not met for PCI.

……..(is this means surgery is a more durable procedure??)

- EXCEL needs longer-term FU (ongoing through 5 years) to examine whether additional differences emerge

Results : EXCEL versus NOBLE

In NOBLE

81% of the patients in NOBLE had bifurcation left main disease, which is more difficult to treat than ostial or trunk left main disease and might be associated with a worse outcome with PCI.

Benefit of CABG was noted in all ranges of the SYNTAX score, which is contrary to the SYNTAX trial in which patients with less complex disease did as well with PCI as with CABG

Surgeons will focus on NOBLE!

while cardiologists will point to EXCEL!

Conclusion and take home message

- Mortality between PCI and CABG were the same in both trials
- The majority of patients with unprotected left main coronary artery disease, can now be managed equally well by means of two strategies of revascularization if carried out by expert, experienced teams.
- NOBLE adds to the level of evidence but is not sufficient by itself to change present guidelines?
- For best long-term sustainable result…which strategy is better ?→ no clear-cut right answer !

Thank You