The left main controversy: is this a real subgroup requiring bespoke clinical recommendations?

Mario Gaudino, MD[1], Domenico Pagano, MD[2], Nick Freemantle, PhD[3].

[1] *Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, NY, USA*
[2] *Department of Cardiothoracic Surgery, University Hospital Birmingham, University of Birmingham, UK*
[3] *Institute of Clinical Trials and Methodology, University College London, UK*

Conflict of interest: MG has nothing to disclose. DP is Secretary General of the European Association for Cardio-Thoracic Surgery, and International Director of the Society of Thoracic Surgeons. The opinions expressed are his own. NF has received funding for consulting from Sanofi Aventis, MSD, AstraZeneca, Takeda, Novo Nordisk, Ipsen, Allergan, PCT. His organisation receives funding from the European Association for Cardio-Thoracic Surgery for methodological and educational work.

Acknowledgement: None.

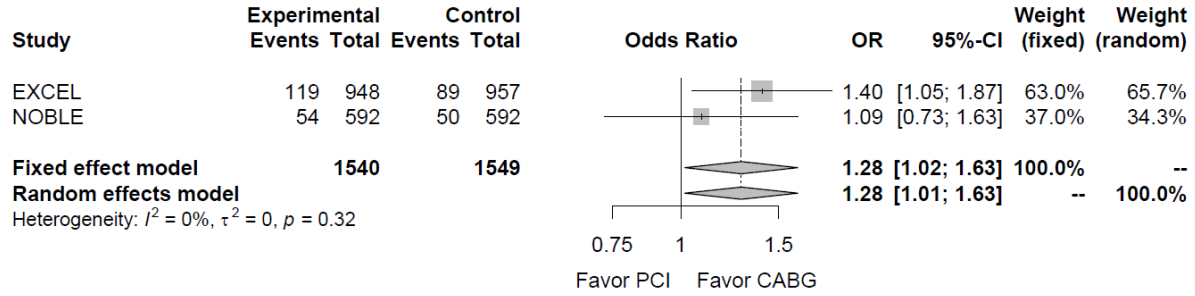
Funding: None.

Text word count: 1220

Address for Correspondence
Mario Gaudino, MD
Department of Cardiothoracic Surgery
Weill Cornell Medicine
525 East 68th Street, New York, NY 10065
Email: mfg9004@med.cornell.edu

Central Message: Left main disease is not a defined biological or statistically discrete subgroup of patients in the current studies, and clinical recommendations on multivessel disease should apply to patients with left main disease.

Central Picture. Meta-analytic estimates for all-cause mortality pooling the EXCEL and NOBLE trials.



For three decades, coronary artery bypass grafting (CABG) has been the standard of care for patients with left main coronary artery stenosis (LMCAS), a practice based on trials which showed improved survival compared to medical management [1]. The Synergy between percutaneous coronary intervention (PCI) with Taxus and Cardiac Surgery (SYNTAX) trial was the first large trial to compare PCI with CABG in the treatment of coronary artery disease [2]. The SYNTAX protocol included a pre-specified exploratory analysis in the subgroup of patients with LMCAS that was underpowered for the primary composite endpoint of all-cause mortality, stroke, myocardial infarction and repeat revascularisation. This subgroup comparison was null at 5-years and generated the hypothesis that, in patients with low and medium coronary disease complexity, the two treatments may achieve similar outcomes [3]. This hypothesis was tested in the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) and Nordic-Baltic-British left main revascularisation (NOBLE) trials [4, 5]. The two trials used different primary composite endpoints [6] and found qualitatively different results. In brief, EXCEL reported no statistically significant difference between CABG and PCI at 5-year follow-up in the primary composite outcome of death from any cause, stroke, or myocardial infarction (including perioperative and spontaneous events). Importantly, all-cause mortality curves diverged in favor of CABG and the difference was nominally significant at 5 years follow up [7]. NOBLE reported a significant advantage of CABG for the primary composite endpoint of all-cause mortality, non-procedural myocardial infarction, repeat revascularisation, and stroke at 5-years, without significant difference in all-cause mortality (although the event rate was low and the confidence interval wide)[8].

Results from these and other trials have been used to underpin clinical guideline recommendations which have considered LMCAS as a separate entity from the rest of the coronary artery disease spectrum [9, 10]. However, the differences in the primary composite outcomes and in the definition of myocardial infarction, with EXCEL adopting an untested primary definition that penalizes surgery in contrast to the best evidence Universal Definition of myocardial infarction [11], as well as a controversy on the validity of the EXCEL trial findings [12, 13], raised doubts on the interpretation of the trial findings and elicited a debate in the cardiovascular community. The European Association for Cardio-Thoracic Surgery (EACTS) withdrew support to the 2018- Myocardial Revascularisation guideline recommendations for the treatment of LMCAS[14]. EACTS took the decision due to a range of scientific, statistical and professional issues raised in the conduct of the EXCEL trial and the guideline process [14]. Other international societies have joined the quest for open data and underlined the importance of transparent analyses [15, 16].

In this issue of *The Journal of Thoracic and Cardiovascular Surgery*, Gallo and colleagues add to the available evidence a trial-level analysis of 5 randomized trials (including SYNTAX, NOBLE and EXCEL) comparing CABG and PCI in the treatment of patients with LMCAS[17,]. The authors report lower early risk of stroke with PCI, but lower risk of repeat revascularization and myocardial infarction with CABG in the first 5 years of follow-up, without statistically significant difference in mortality (although the pooled estimate numerically favors CABG at 5 years). The results are consistent with another, widely publicized, recently published trial-level meta-analysis [18].

An appropriate approach to address the controversy would be to establish whether current evidence supports the premise that LMCAS is a separate entity within the coronary artery

disease spectrum, thus requiring a bespoke clinical treatment strategy. For this to be true, we would require LMCAS to be a defined biological and statistical subgroup.

A recent patient level meta-analysis by Head et al is enlightening [19]. The authors included 11,518 patients (4478 with LMCAS) from 11 randomised trials of CABG vs PCI including SYNTAX, EXCEL and NOBLE with a mean follow up of 3.8 years to compare the all-cause mortality between CABG and PCI. Head and colleagues found a significant survival disadvantage for PCI over CABG for the overall cohort (hazard ratio [HR] 1.20, 95% confidence interval [CI] 1.06 to 1.37; p=0.004). A careful evaluation of the subgroup analysis reveals that LMCAS could not be described as a statistically separate entity, as comparison for treatment effect between the main cohort and the subgroup with LMCAS was not significant (P for interaction= 0.12)[20] which suggests that a recommendation for this clinical scenario should reflect the overall results of the study .

Suggesting that LMCAS is a separate entity is further complicated, because in most reported trials the majority of patients with LMCAS also have coronary disease affecting other vessels and the incidence of isolated LMCAS is only between 12.9% and 14.6% [7, 21, 22], rates which seem to be reflected in real world clinical practice [23]. Head et al also described that there was a significant overlap between LMCAS and multivessel disease in their analysis [22].

In summary, LMCAS is rarely a discrete biological entity, and it is unclear what mechanisms might be considered associated with treatment effect modifications in patients who have LMCAS (most often alongside multi-vessel disease) compared to patients with other forms of coronary artery disease.

As isolated LMCAS is an uncommon clinical entity, it would be challenging, and likely impossible, to design clinical trials for this group with clinically relevant endpoints.

In summary, the population studied in trials of LMCAS does not reflect a defined biological or statistically discrete subgroup of patients. This suggests that we should not pursue clinical recommendations for the treatment of isolated LMCAS, but instead should apply the recommendations of the combined left main and multivessel coronary disease to this group, which in patients with acceptable surgical risk favors CABG.

The results of randomised trials reflect both the effects of treatment and crucially the play of chance (the way in which patients are allocated between treatment groups). In low-powered circumstances, chance may lead to substantial numerical differences between estimated treatment effects, as in the difference between NOBLE and EXCEL all-cause mortality at 5 years. Composite outcomes can increase the number of available events and thus strengthen the conclusions. The 5 years composite outcome results for both NOBLE (HR 1.58, 95% CI 1.24 to 2.01; p=0·0002) and EXCEL (when the unpublished Universal Definition is used[12]: HR 1.40, 95% CI 1.09 to 1.81; p= 0.009) are significantly in favor of CABG.

It has been proposed that meta-analysis of the LMCAS trials could be helpful in resolving the controversy. Unfortunately, this approach would address only part of the problem, allowing an examination of the results of the LMCAS subgroup, but not an analysis of the role of LMCAS among patients with multivessel coronary disease. Instead, an appropriate methodological approach would include all trials for PCI versus CABG and use multivariable analyses to examine the interaction of different disease characteristics, including LMCAS, with treatment on the outcome.

Also, as neutral results in the earlier underpowered trials led to the LMCAS hypothesis being tested in NOBLE and EXCEL, including those hypothesis-forming trials in any meta-analysis is a

source of selection bias. A pooled analysis should include only the confirmatory trials (NOBLE and EXCEL). The results of this analysis (using the published EXCEL data) are provided in the Central Picture and show superiority of CABG for mortality at 5 year follow up; this is, at the moment, the best available answer to the LMCAS controversy.

REFERENCES

1. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *The Lancet.* 1994;344:563-570.

2. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360:961-972.

3. Morice M-C, 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;129:2388-2394.

4. Kappetein AP, Serruys PW, Sabik JF, et al. Design and rationale for a randomised comparison of everolimus-eluting stents and coronary artery bypass graft surgery in selected patients with left main coronary artery disease: the EXCEL trial. *EuroIntervention.* 2016;12:861-872.

5. Mäkikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *The Lancet.* 2016;388:2743-2752.

6. Ruel M, Farkouh ME. Why NOBLE and EXCEL Are Consistent With Each Other and With Previous Trials. *Circulation.* 2017;135:822-824.

7. Stone GW, Kappetein AP, Sabik JF, et al. Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease. *N Engl J Med.* 2019;381:1820-1830.

8. Holm NR, Makikallio T, Lindsay MM, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. *The Lancet.* 2020;395:191-199.

9. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.

10. 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. *JACC.* 2012;60:e44-e164.

11. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation.* 2012;126:2020-2035.

12. BBC Newsnight. European guidelines on heart disease under review. [Available from https://youtu.be/_vGfJKMbpp8] (Accessed on April 14, 2020)

13. TCTMD. EXCEL Investigators Respond to Data Suppression Claims as Debate Erupts Online 2020 [Available from: https://www.tctmd.com/news/excel-investigators-respond-data-suppression-claims-debate-erupts-online] (Accessed on April 14, 2020)

14. EACTS. Changing Evidence, Changing Practice 2019 [Available from: https://www.eacts.org/changing-evidence-changing-practice] (Accessed on April 14, 2020)
15. STS. STS Statement on Recent Left Main Randomized Trials 2020 [Available from: https://www.sts.org/media/news-releases/sts-statement-recent-left-main-randomized-trials] (Accessed on April 14, 2020)
16. AATS. AATS Statement on Transparency of Clinical Research Data 2019 [Available from: https://www.aats.org/aatsimis/AATSWeb/Association/About/Statement%20ESC-EACTS.aspx] (Accessed on April 14, 2020)
17. Gallo M, Blitzer D, Laforgia PL, et al. PCI vs. CABG for left main coronary artery disease: a meta-analysis. *J Thorac Cardiovasc Surg.* 2020;In press.
18. Ahmad Y, Howard JP, Arnold AD, et al. Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: a meta-analysis of randomized controlled trials. *Eur Heart J.* 2020. pii: ehaa135.
19. Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *The Lancet.* 2018;391:939-948.
20. Freemantle N, Ruel M, Gaudino MFL, Pagano D. On the pooling and subgrouping of data from percutaneous coronary intervention versus coronary artery bypass grafting trials: a call to circumspection. *Eur J Cardiothorac Surg.* 2018;53:915-918.
21. Thuijs DJFM, Kappetein AP, Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *The Lancet.* 2019;394:1325-1334.
22. Head SJ, Papageorgiou G, Milojevic M, Stone GW, Kappetein AP. Interpretation of results of pooled analysis of individual patient data - Authors' reply. *The Lancet.* 2018;392:818.
23. Taylor HA, Deumite NJ, Chaitman BR, Davis KB, Killip T, Rogers WJ. Asymptomatic left main coronary artery disease in the Coronary Artery Surgery Study (CASS) registry. *Circulation.* 1989;79:1171-1179.