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Editorial

Left main percutaneous coronary intervention *versus* coronary artery bypass surgery: A case of true equivalence in low and intermediate complexity anatomy or a question yet to be answered?

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In the current issue of *Atherosclerosis*, Zhang et al. present a meta-analysis of 4 randomized control trials (RCT) comparing the efficacy of coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) in patients with left main coronary artery disease (LMCAD) [1]. Despite the controversy that ensued after the publication of the five-year results of the EXCEL trial [2], the cumulative clinical outcomes reported therein reinforced the notion that revascularization of LMCAD with PCI in patients with low and intermediate complexity anatomy is an acceptable, safe and durable alternative to CABG. Moreover, ten-year follow up data of the SYNTAX trial [3] showed comparable all-cause mortality between PCI and CABG, in patients with left main disease, regardless of SYNTAX score. While the 5-year data from the NOBLE trial [4] showed superiority for CABG over PCI in patients with left main disease and low or intermediate syntax scores, it was driven primarily by the need for repeat revascularization and non-fatal myocardial infarction (MI), while peri-procedural MI - which was in favor of PCI in the EXCEL trial - was not included in the event analysis. Importantly, the incidence of cardiovascular mortality and stroke in both landmark trials was similar between PCI and CABG. Accordingly, the European guidelines have given a I and IIa recommendation for PCI in patients with LMCAD with low and intermediate anatomical complexity, respectively [5]. Despite this, in the US there are no updated guidelines for this population, which is reflected in the paltry number of patients who currently undergo unprotected left main PCI (ULMPCI). A recent analysis of the National Cardiovascular Data Registry revealed that ULMPCI accounts for only 1% of all PCIs [6]. (see Table 1).

In total, data from 4394 patients were included, with 2197 in each respective arm. Only trials that were randomized in design, mandated the use of drug eluting stents (DES), and had a follow up of 5 years or more were included in the analysis. Overall, the authors showed that CABG, in all comers, had an advantage over PCI in terms of their primary outcome, major adverse cardiovascular events (MACCE) (HR 1.48, 95% CI 1.25–1.75), which was driven by the need for repeat revascularization. Interestingly, however, the secondary outcome (a composite of death, myocardial infarction and stroke) did not differ among groups (HR 1.22, 95% CI 0.84–1.75, RR 1.15, 95% CI 0.93–1.44). Additionally, their sub-group analysis of patients with low-intermediate syntax scores showed comparable outcomes between groups (HR 1.29, 95% CI 0.85–1.70).

Zhiang et al. performed an extensive literature review that included 9779 articles, only 4 of which met inclusion criteria, with all being high quality in their design and reflecting contemporary left main PCI, thus improving the external validity of their analysis to current practice [1]. While the topic and data presented are not novel, the way the analysis of the data was conducted is novel. Random effect models were used to calculate hazard and risk ratios, in addition to cumulative Kaplan-Meier survival curves for summary measures. The methodology, design and statistical methods performed are also in line with high academic standards and previously published meta-analyses on the topic. Furthermore, their findings mirror contemporary meta-analyses of patient level data in this population [7,8].

As mentioned, the article is a meta-analysis of summary statistics rather than individual patient level data; thereby making it difficult to minimize heterogeneity between studies, in addition to adequately adjusting for potential confounders. Specifically, the NOBLE trial, as pointed out by the authors, did not include peri-procedural MI as a clinically relevant event, while the other RCTs did. The presence and frequency of three vessel CAD were not available in three of the trials included, adding further to the heterogeneity and potential for confounding. Furthermore, the authors used two similar primary and secondary endpoints in their protocol, the first being MACCE and the second being a composite of mortality from any cause, MI and stroke, which may allude to an element of *post hoc* reporting bias.

In summary, this contemporary meta-analysis reports CABG as being

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Table 1
Summary measures from contemporary LM revascularization articles.

	Trial design	**No. of patients** included	**Death:** PCI *vs.* CABG	**Stroke:** PCI *vs.* CABG	**MI:** PCI *vs.* CABG	**Revascularization:** PCI *vs.* CABG	**Composite primary endpoint:** PCI *vs.* CABG
Syntax-10 yr	RCT	1800	HR 1.19(CI 0.99–1.42)	NA	NA	NA	See death
Precombat-10 yr	RCT	600	14.5 *vs.* 13.8%, HR 1.13 (CI 0.75–1.70)	1.9 *vs.* 2.2% HR 0.71 (CI 0.22–2.23)	3.2 *vs.* 2.8% HR 0.76 (CI 0.32–1.82)	16.1% *vs.* 8% HR1.98 (CI 1.21–3.21)[a]	HR 1.25 (CI, 0.93–1.69)
Excel-5yr	RCT	1905	13 *vs.* 9.9% OR 1.38 (CI 1.03–1.85)[a]	2.9 *vs.* 3.7% OR 0.78 (CI 0.46–1.31)	10.6 *vs.* 9.1% 1.14 (0.84–1.55)	17.2% *vs.* 10.5% OR 1.79 (CI 1.36–2.36)[a]	22% *vs.* 19.2% OR 1.19 (0.95–1.50)
Nobel-5yr	RCT	1201	9 *vs.* 9% HR 1.08 (CI 0.74–1.59)	4% *vs.* 2% HR 1.75 (0.86–3.55)	NA	17 *vs.* 10% HR 1.73 (1.25–2.40)[a]	28 *vs.* 19% HR 1.58 (CI 1.24–2.01)[a]
Boudriot et al.	RCT	201	2 *vs.* 5% (CI -9.4–2.7)	NA	3 *vs.* 3% (CI -5.8–5.9)	14 *vs.* 6% (CI -0.3 to 17.1)[a]	19 *vs.* 14% (−5.3 – 15.7)
Ahmad et al.	Meta-analysis	4612	RR 1.03 (CI 0.82–1.32)	RR 0.74 (CI 0.36–1.50)	RR 1.22 (CI 0.96–1.56)	RR 1.73 (CI 1.49–2.02)[a]	See death
Zhang et al.	Meta-analysis	4394	HR 1.06 (CI 0.81–1.40)	HR 0.80 (CI 0.42–1.53)	HR 1.59 (CI 0.93–2.73)	HR 1.76 (CI 1.48–2.10)[a]	HR 1.22 (CI 0.84–1.75)
Head et al.	Meta-analysis	11,518	HR 1.20 (CI 1.06–1.37)[a]	NA	NA	NA	See death
Palmerinini et al.	Meta-analysis	4686	HR 0.99 (CI 0.76–1.30)	HR 0.71 (CI 0.34–1.49)	HR 1.33 (0.84–2.11)	HR 1.27 (1.12–1.45)[a]	HR 1.06 (CI 0.82–1.37)

RR = relative risk; OR = odds ratio; RCT = randomized control trial.
[a] Denotes outcomes where CABG had a statistically significant benefit over PCI.

superior to PCI when it comes to revascularization of LMCAD with associated high anatomical complexity. It also adds to a well-established body of evidence that now supports an equipoise between PCI and CABG in patients with LMCAD and low to intermediate SYNTAX scores.

While the recent controversy over the EXCEL trial surrounded the definition of peri-procedural myocardial infarction and its subsequent weight in the composite primary endpoint, little credence has been given to another controversial aspect of endpoint adjudication: time-to-event analysis. In time-to-event analysis, only the first event in each arm is counted as part of a given composite endpoint, regardless of its clinical significance. Competing risk, represented by further events, regardless of their severity, can then also be lost or not counted in patients who have died. Interestingly, when a novel statistical method that weighted endpoints based on clinical significance was used to perform a *post-hoc* analysis of the DELTA registry, equivalence was found between PCI and CABG in patients with LMCAD [9]. While inadequate adjudication of peri-procedural MI could confound a composite endpoint, so too will a poorly weighted composite endpoint.

With the implementation of coronary physiology and mandated intra-coronary imaging optimization, cumulative outcomes after PCI in the single arm SYNTAX II trial were significantly lower when compared with the original SYNTAX I PCI cohort (13.2% *vs.* 21.9%) [10]. Moreover, equipoise was also observed when the same contemporary cohort was compared with the original SYNTAX CABG cohort, albeit in patients with three vessel CAD and not LMCAD (13.2% *vs.* 21.9%). A recently published sub-study of the NOBLE trial showed that target vessel revascularization (TLR) was significantly reduced in the cohort of patients who had intra-vascular ultrasound (IVUS)-guided ULMPCI compared with those who did not [11]. Impressively, in this cohort, none of the patients who had a minimum stent area (MSA) greater than 13.4 mm^2 post PCI required TLR at 5-year follow-up. IVUS guidance and optimization for LMPCI have a direct effect on the predominant endpoint, within the composite that drives the superiority of CABG in trials, but was not mandated in all patients randomized in previous trials.

Updated American guidelines are now needed to reflect the ample evidence supporting LMCAD revascularization with PCI, in addition to encourage increased utilization of PCI, in what is an underserved patient population. Future trials, mandating intra-coronary imaging and physiology in their protocols, are necessary. Ideally, these trials should also implement homogenous endpoint definitions in addition to implementing novel and contemporary methods for cumulative weighted adjudication of outcomes in long-term follow-up. Both strategies will likely elucidate a truer reflection of high-quality contemporary PCI in this setting, when compared to CABG, which is evolving with resultant improved outcomes [12]. Most importantly, a clear and reflective explanation of the evidence needs to be given to each patient, so that shared decision-making and autonomy are preserved. The possible need for unplanned revascularization in patients undergoing PCI may not be a large deterrent for many when compared to undergoing CABG, but we will never know unless we ask.

Conflicts of interest

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