Editorial

PCI or CABG for unprotected left main coronary artery disease?—new evidence justifies a change in perspective

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Unprotected left main coronary artery disease (ULMD) is associated with an adverse prognosis (1,2). It was demonstrated almost a quarter of a century ago that patients with ULMD derive long-term prognostic benefit from coronary artery bypass graft surgery (CABG) compared with conservative treatment (3). The advent of coronary artery stenting quickly saw percutaneous coronary intervention (PCI) overtake CABG as the most commonly performed myocardial revascularisation procedure in patients with coronary artery disease as a whole (4). Only recently, however, has PCI been considered a genuine alternative to CABG for patients who have ULMD. This change in perspective arose due to improvements in balloon and stent technologies which facilitated complex PCI, pioneering PCI operators who brought ULMD PCI into mainstream clinical practice, and increasing evidence that PCI achieves favourable clinical outcomes in patients with ULMD.

Until recently, the main randomised controlled trial data comparing PCI with CABG to treat patients with ULMD came from the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) study and the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial (5,6). Five-year rates of major adverse cardiac and cerebrovascular events (MACCE) in the SYNTAX study were not significantly different following PCI and CABG (36.9% *vs.* 31.0%; P=0.12) in patients with ULMD. Repeat revascularisation was more frequent (26.7% *vs.* 15.5%; P=0.01) in patients who were allocated to PCI than CABG, but rates of all-cause mortality and MI were no different, and stroke was significantly less common (1.5% *vs.* 4.3%; P=0.03) in PCI patients. The PRECOMBAT trial consolidated the results of the SYNTAX study in showing that PCI achieved similar rates to CABG of MACCE (17.5% *vs.* 14.3%; P=0.26) but PCI was associated with higher rates of ischaemia-driven target vessel revascularisation (TVR) (11.4% *vs.* 5.5%; P=0.012). Both studies reported clinical outcomes stratified by tertiles of coronary artery lesion complexity (for PCI) as measured by the SYNTAX score. In the SYNTAX study, patients in the lower two tertiles (SYNTAX score ≤32) faired equally well for MACCE following PCI or CABG; in fact, death was significantly less common (7.9% *vs.* 15.1%; P=0.02) after PCI. By contrast, patients in the upper tertile of SYTNAX score (≥33) had higher rates of MACCE at 5 years (46.5% *vs.* 29.7%; P=0.003), including the individual end-points of cardiac death (15.8% *vs.* 5.9%; P=0.006) and repeat revascularisation (34.1% *vs.* 11.6%; P<0.001) after PCI than after CABG. In the PRECOMBAT trial, ischaemia-driven TVR was significantly more common after PCI than after CABG in patients with SYNTAX scores ≥33, but the relative efficacy of PCI and CABG for death, MI or stroke was not influenced by SYNTAX score. These findings are reflected in current clinical practice guidelines for myocardial revascularisation which recommend CABG

for patients with ULMD and a SYNTAX score ≥33, but recognise PCI as an alternative to CABG in patients with lower SYNTAX scores (7). Despite this, in most cardiac centres CABG remains the default management strategy for treating ULMD irrespective of disease complexity. This relates partly to the historical precedence of CABG over PCI and partly to lingering doubts regarding the ability of PCI to achieve long-term event-free survival comparable with CABG in treating the left main stem.

The evidence base in this area was bolstered in October 2016 by the publication of two important new trials. EXCEL (The Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial) and NOBLE (The Nordic-Baltic-British Left Main Revascularisation study) enrolled 1,905 and 1,184 patients, respectively, more than doubling the number of patients who have been included in randomised controlled trials of PCI compared with CABG to treat ULMD (8,9). Both were non-inferiority trials. At first glance, the primary results were contradictory; EXCEL showed that PCI was non-inferior to CABG while NOBLE showed that CABG was superior to PCI! Closer analysis of the trials revealed several explanations for these apparently inconsistent results, which related mainly to differences in the composition of the combined primary endpoints and to different definitions of MI between the two trials.

In order to clarify the relative efficacy of PCI and CABG in patients with ULMD, Mahmoud and colleagues undertook a meta-analysis of six randomised trials comparing the two revascularisation strategies in this group of patients (10). The findings are worthy of comment, not least because they are likely to influence clinical decision making and consolidate the shift towards PCI in this patient group. The meta-analysis included 4,700 patients and incorporated the four main contemporary randomised trials of PCI compared with CABG in patients with ULMD, SYNTAX, PRECOMBAT, EXCEL, and NOBLE. Weighted incidences and risk ratios (RR) with 95% confidence intervals (CI) were calculated for clinical outcomes at 30-days, 1-year, and 5-year follow-up. At 30 days, PCI was associated with a significantly lower risk of MACCE (3.9% *vs.* 7.3%; RR 0.55, 95% CI: 0.39–0.76), MI (2.3% *vs.* 4.9%; RR 0.67, 95% CI: 0.46–0.99), and stroke (0.4% *vs.* 1.2%; RR 0.38, 95% CI: 0.16–0.90) than CABG. At 1 year, the frequency of stroke remained lower after PCI than after CABG, but the rate of repeat revascularisation was significantly higher. At 5 years, the incidence of MACCE was significantly higher after PCI than after CABG (23.9% *vs.* 19.3%; RR 1.19, 95% CI: 1.01–1.41). There were no significant differences in five-year rates of all-cause mortality (6.7% *vs.* 6.7%; RR 0.94, 95% CI: 0.73–1.22), MI (6.2% *vs.* 5.1%; RR 1.39, 95% CI: 0.86–2.25), or stroke (2.0% *vs.* 2.3%; RR 0.86, 95% CI: 0.44–1.68) between PCI and CABG groups. Repeat revascularisation, however, was significantly more common (12% *vs.* 7.4%; RR 1.62, 95% CI: 1.34–1.94) 5 years after PCI than after CABG.

The publication of NOBLE and EXCEL greatly strengthened the evidence base regarding the relative efficacy of PCI and CABG for treating patients with ULMD. The results of Mahmoud *et al.'s* meta-analysis, which included both of these studies, suggest that patients with left main disease who undergo PCI achieve similar five-year rates of mortality, MI and stroke as patients who undergo CABG. One of the main concerns regarding the use of PCI to treat ULMD is the risk of stent thrombosis, since it carries potentially catastrophic consequences in this anatomical location. There has been considerable debate over the last 10 years regarding the risk of stent thrombosis associated with different stent types. Late stent thrombosis, in particular, occurs more frequently with the use of first generation DES compared with bare metal stents (BMS) (11). Contemporary DES use lowers the rate of stent thrombosis compared with first generation DES or BMS use (12). Whether or not biodegradable polymer (BP) DES use is associated with lower rates of long-term stent thrombosis than contemporary durable polymer (DP) DES use remains uncertain. A meta-analysis of five randomised controlled trials (4,687 patients) which compared BP DES with DP DES reported lower rates of definite or probable stent thrombosis after 5 years in patients who received BP DES (13). However, the difference was limited to patients who were treated with first generation DP DES; there was no difference in rates of stent thrombosis between patients who received second generation DP DES or BP DES. In Mahmoud's meta-analysis, rates of stent thrombosis were reported in three trials (SYNTAX, EXCEL, and NOBLE). Stent thrombosis occurred in 2.1% patients, compared with 3.8% who experienced symptomatic graft occlusion (RR 0.56; 95% CI: 0.22–1.44). Different types of stent were used in each of the three trials; one used a first-generation DP based paclitaxel DES, one used a newer generation DP everolimus based DES and one used a BP biolimus DES. It was not possible to determine if there was a difference between stent types in the risk of stent thrombosis. Nor were the direct clinical consequences of these events clear

from the data, but serious adverse clinical outcomes would be recorded amongst the trial clinical endpoints, which showed no differences in rates of death or MI following PCI compared with CABG at 5 years. In fact, PCI was associated with lower rates of MI at 30 days and lower rates of stroke after 30 days and after 1 year compared with CABG. These findings are reassuring regarding the safety and efficacy of PCI in treating patients with ULMD. Indeed, PCI might be preferable to CABG in patients who are at high risk of perioperative stroke or MI.

These trials of myocardial revascularisation illustrate the importance of the choice of study endpoints and how this can impact upon the interpretation of trial results. The EXCEL investigators selected all-cause mortality, MI, or stroke as their combined primary endpoint while the NOBLE investigators also included repeat revascularisation in theirs. In EXCEL, death, MI, or stroke at three years occurred in 15.4% of patients in the PCI group and in 14.7% of patients in the CABG group (P=0.02 for non-inferiority; P=0.98 for superiority) or, put another way, PCI achieved equivalent results to CABG for these "safety" endpoints. In NOBLE, Kaplan-Meier five-year estimates of MACCE were 29% for PCI and 19% for CABG, exceeding the limit for non-inferiority, and CABG was significantly better than PCI (P=0.0066). The most common clinical event after PCI or CABG is repeat revascularisation. It is established that repeat revascularisation rates are higher following PCI than after CABG, with up to a three-fold difference, in patients treated for multi-vessel disease (14). The widespread availability of DES has reduced rates of restenosis, one of the main drivers for repeat revascularisation after PCI, but PCI does not mitigate the effects of the development of new disease proximal to the points at which grafts would be anastomosed in patients treated by CABG (15,16). In this meta-analysis, CABG reduced the risk of repeat revascularisation at five years by 58% compared with PCI. However, the requirement for repeat revascularisation was low after either procedure. Furthermore, in most cases (about 80% in NOBLE and EXCEL), repeat revascularisation after PCI is by further PCI rather than by CABG. Whether or not lowering the absolute risk of repeat revascularisation by <5% after CABG compared with PCI is sufficient to justify the greater upfront risks and more invasive nature of surgery can be left for patients to decide.

It was not clear from this meta-analysis, which was limited by its lack of patient-level data, if particular patient subgroups gained a preferential benefit from PCI or CABG. Random effects regression meta-analyses showed no significant interaction between any of age, distal left main stenosis, acute coronary syndrome, diabetes, gender, antiplatelet use, chronic kidney disease, complete revascularization, mean SYNTAX score or mean EURO score in the PCI group, and clinical outcome rates in PCI and CABG groups. Intuitively, patients who have a high SYNTAX score would be expected to derive the greatest benefit from CABG by reducing the risk of repeat revascularisation (and thereby MACCE) but the differential treatment effect on MACCE which was observed in the SYNTAX study and the PRECOMBAT trial was not replicated in the larger trials of NOBLE or EXCEL. A differential treatment effect according to disease complexity might have been masked in NOBLE by modest numbers of patients (102, or 9% of the study population) who had a SYNTAX score ≥33. In EXCEL, patients with a SYNTAX score ≥33 (as assessed by the on-site heart team) were excluded from the study. In fact, when assessed by the core laboratory, 446 (24.2%) of the randomised patients had a SYNTAX score ≥33. Nevertheless, there was no interaction between SYNTAX score and the relative efficacy of PCI and CABG for MACCE. Furthermore, amongst 393 patients who underwent everolimus DES implantation for ULMD at a single centre, neither restenosis rates nor three-year cardiac mortality were significantly different in patients whose SYNTAX scores were ≥33 compared with <33 (17).

Notwithstanding the positive clinical outcomes achieved by PCI in this meta-analysis, it is incumbent on PCI operators to achieve optimal stent expansion in order to minimise the risk of stent thrombosis and restenosis, both of which are directly related to stent cross-sectional area (18,19). The use of intravascular ultrasound (IVUS) has been advocated for several years as an important tool for optimising PCI procedural results in patients with ULMD. The results of a recent analysis of 10 studies (nine observational and one randomised) which compared clinical outcomes in patients who underwent ULMD PCI with or without the use of IVUS supports this recommendation (20). Amongst 6,480 patients, IVUS-guided PCI was associated with significantly lower risks of all-cause death (RR 0.60, 95% CI: 0.47–0.75, P<0.001), cardiac death (RR 0.47, 95% CI: 0.33–0.66, P<0.001), target lesion revascularization (TLR) (RR 0.43, 95% CI: 0.25–0.73, P=0.002), and stent thrombosis (RR 0.28, 95% CI: 0.12–0.67, P=0.004) compared with angiography-guided PCI. The mechanism through which IVUS use improved outcomes was not elucidated. IVUS can be used to assess plaque burden

in the distal left main stem and the ostia of its branches, the presence and severity of calcification, and vessel size. Thus, IVUS provides information which guides lesion preparation, stent strategy, and stent selection. Its main influence, however, is probably to encourage effective post-dilatation (21). Nationwide registry data showed that IVUS was used in 44% of ULMD PCI cases in the UK in 2015 (4). The rates of IVUS use in NOBLE and EXCEL were 74% and 77%, respectively. Targeting IVUS rates of closer to 100% is an obvious way through which clinical outcomes might be improved after ULMD PCI. Performing the procedure through the radial artery offers further clinical gains, yet this route of arterial access was used in only 27% of cases in EXCEL. Whether or not a specific technique should be used for stenting the left main stem is not clear. The majority of cases involve the bifurcation of the left main stem. Provisional stenting of the side branch is the technique of choice for most bifurcation lesions (22,23). However, a recent randomised controlled trial of 482 patients who had true distal left main stem bifurcation lesions (Medina 1,1,1 or 0,1,1) found that the double kissing (DK) crush two-stent technique achieved lower 12-month rates of target lesion failure, target vessel MI, and definite or probable stent thrombosis than provisional stenting. Rates of clinically driven TLR, angiographic restenosis, and cardiac death were not significantly different between groups (24). Irrespective of stent strategy, use of the proximal optimisation technique (POT), in which a short balloon is used to post-dilate the proximal main branch to the carina, is encouraged at the end of the procedure in order to optimise stent expansion in the main branch and preserve the bifurcation anatomy (25).

In summary, patients with ULMD who were entered in to six randomised controlled trials achieved similar rates of death, MI, or stroke 5 years after allocation to PCI or CABG. Patients in the PCI group were more likely to require repeat revascularisation, usually by further PCI. Most patients required treatment of a distal left main bifurcation lesion and one or two further lesions. In NOBLE, which presented detailed information about the PCI procedures, left main bifurcation stenting was performed in 88% of cases, the majority (59%) by deploying a stent from the left main stem into the left anterior descending artery. About a third of patients had a second lesion treated (usually with one stent), and 10% of patients had a third lesion treated. In EXCEL, treatment of the left main stem and one additional lesion was the most frequent PCI procedure, using a mean of 2.4 stents and a total stent length of 49 mm. In these types of patients, PCI should be seen as a genuine alternative to CABG. Both PCI and CABG should be offered unless there are factors which mitigate against a good procedural result or an uneventful recovery for one (or both) of them. There are no trials listed in the main clinical research registers which investigate the efficacy of PCI compared with CABG in patients who have ULMD and additional complex disease which would require treatment of long lengths of disease, second true bifurcation lesions, or chronic total occlusions. For the foreseeable future, therefore, decisions regarding their management will be made on a patient-by-patient basis, guided by the heart team.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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