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Chronic coronary syndromes – Time to reassess the evidence?

The first half of 2018 has seen no less than 6 high-impact publications on stable coronary artery disease (CAD)/chronic coronary syndromes (CCS). Some of these have questioned, and others will potentially redefine, our practice in the management of this patient cohort.[1-6] ORIBITA, the first interventional placebo controlled trial to assess the effect of invasive management in stable CAD exploded onto the scene in January 2018, questioning the validity of percutaneous coronary intervention (PCI) in this patient subset.[1] It led to a firestorm of commentary in the world of "twitter cardiology" and encouraged the authors of the accompanying editorial to provocatively title their manuscript: "Last nail in the coffin for PCI in stable angina?"[7]

To date, PCI vs. optimal medical therapy (OMT) for stable CAD has never been proven to provide clinical benefit in terms of hard outcomes, particularly cardiac death or myocardial infarction (MI). The extended-follow-up of COURAGE has provided up to 15-years of data in this regard.[8] For individuals with stable CAD, randomised to either PCI + OMT or OMT alone, for all its shortcomings, COURAGE has provided us with evidence that cannot be ignored, PCI does not influence hard endpoints.[8] One particularly important shortfall of COURAGE was that participants were randomised after having been evaluated for ischaemia. This resulted in the potential for selection bias whereby patients with a high burden of ischaemia would most likely not have been included. ISCHAEMIA, which is still enrolling and the results of which are planned for release in 2020, was designed to address this particular oversight in the COURAGE trial design: patients being randomised prior to ischaemia testing.[9]

The dogma that in stable CAD, PCI provides relief of angina in patients that have failed OMT, but that it falls short of protecting against MI, or preventing death, has more recently been challenged.[3,10] However, given that the majority of MIs occur secondary to plaque rupture of non-flow limiting lesions that would ordinarily not have been targets for PCI in individuals with stable CAD, this finding does not quite make sense. It has a weak scientific foundation; persistent endothelial inflammation leads to the rupture of predominantly non-flow limiting thin-capped vulnerable, and not thick-capped stable, plaques.

In patients with single-vessel stable CAD, randomised to either PCI + OMT or Sham-PCI + OMT, ORBITA questioned the validity of PCI, previously established in unblinded observational and randomised controlled studies to provide symptomatic relief. The investigators chose, as their primary endpoint, a difference in exercise time evaluated 6 weeks post PCI, an endpoint that has been well validated in placebo-controlled trials of pharmacotherapy in stable CAD. This was a robustly conducted study; all participants had a 6 week lead-in period of aggressive anti-

anginal therapy including ≥2 anti-anginal medications. At 6 weeks, prior to randomisation to PCI + OMT or alternatively Sham-PCI + OMT, 98% had class II/III angina. They also underwent a modified Bruce protocol cardiopulmonary exercise test, completed an angina questionnaire and were evaluated by dobutamine stress echocardiography (DSE). PCI did not improve the primary endpoint of exercise time compared to Sham-PCI, bringing into question the potential placebo effect of undergoing an invasive procedure.[1] It is well established that invasive procedures provide a more marked placebo effect than non-invasive interventions and this seemed to hold true for PCI in single-vessel stable CAD, or did it?

During the trial, 98% of participants had a research based invasive physiology assessment by FFR and iFR after randomisation and prior to PCI / Sham-PCI. Both the interventional operator and managing clinician were blinded to these results so as not to influence therapy assignment. In a recently released physiology-stratified sub-analysis of the ORBITA cohort, PCI resulted in a significant reduction in patient reported angina, i.e. complete resolution of symptoms, compared to the placebo group.[2] Surely this is exactly what we set out to achieve in the management of such patients in our daily clinical practice? An association between a dichotomous FFR/iFR cut-point and freedom form angina could not be defined. PCI also resulted in a marked reduction in ischaemia, measured by the assessment of pre- and post-PCI DSEs by no less than 6 different imaging cardiologists to provide adequate power. The degree of improvement in wall motion score at DSE was associated with the absolute FFR, or iFR value, with more marked improvements at lower FFR/iFR. With a NNT=5 to provide patients with freedom from angina, the value of PCI in individuals with single-vessel stable CAD who have failed OMT has been vindicated.[2] In the words of Jedi master Yoda of Star Wars: "Balance has been restored to the force".

Justifiably, PCI therefore remains an important component of our armamentarium in the management of stable angina in patients who fail OMT. Could it, however, offer more than just symptom relief? The release of 4 late breaking trials, including the physiology stratified sub-analysis of ORBITA, last month at EuroPCR prompted PCR to release a statement on Chronic Coronary Syndromes through the European Society of Cardiology's Press Office.[10] In essence, the statement suggested that there is evidence to support FFR-guided PCI in stable CAD to impact hard clinical outcomes and not just target symptoms. Three important studies include: The Five-Year FAME-2 analysis (RCT of FFR-guided PCI + OMT vs. OMT), a patient-level pooled analysis of FAME-2, COMPARE-ACUTE and DANAMI-3-PRIMULTI (studies that have prospectively evaluated FFR-guided PCI of stable lesions with contemporary stents) and observational registry data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).

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The first of the 3 has been published, we await publication of the latter 2. The prespecified Five-Year analysis of FAME-2 has revealed that FFR-guided PCI + OMT vs. OMT in stable CAD is superior in terms of a composite primary endpoint of all-cause mortality, MI and urgent revascularisation (UR).[3] This difference was driven by UR, an outcome that is not difficult to understand given that patients, physicians and nurses were aware of the assigned treatment. The curves for UR diverge immediately after randomisation to PCI or OMT and this undoubtedly provides a degree of selection bias, most patients who did not receive PCI probably did not sleep very well at night. By the end of the 5-year period 51% in the OMT group had crossed over to PCI. In a landmark analysis FFR-guided PCI provided for a marginally lower rate of MI (8.1% vs. 12%; HR 0.66, P=0.49), for spontaneous and not peri-procedural MI. This finding goes against the general observation that most MIs occur secondary to non-flow limiting plaque rupture, and further analysis will be required to ascertain whether or not spontaneous MIs were within the artery of interest, or occurred elsewhere.[3]

Neither FAME-2, COMPARE-ACUTE nor DANAMI-3-PRIMULTI was individually adequately powered to detect differences in cardiac death or MI between OMT and FFR-guided PCI. A patient-level pooled analysis of the 3, presented at EuroPCR and not yet published, is the first to provide evidence in favour of a reduction in cardiac death and MI. An important question that we need to ask though is whether or not these results can be extrapolated to the general stable CAD population? Other than FAME-2, these studies assessed FFR-guided PCI of non-culprit lesions in patients undergoing invasive therapy for ST-segment elevation myocardial infarction (STEMI), and not stable CAD. Interestingly, taken on their own neither could provide for a reduction in cardiac death or MI. The advantage of FFR-guided PCI of presumably stable non-culprit lesions, in the setting of a recent STEMI, was once again a reduction in the need for symptom driven revascularisation after PCI of the culprit.

Considering the limitations of the currently available data, it may be premature to declare that FFR-guided PCI in stable CAD provides for a reduction in hard clinical endpoints. It does, however, address the need for urgent revascularisation; even then, in the truly stable CAD cohort this applies to patients who were not blinded to their initial treatment assignment.

In patients with multivessel (MVD) stable CAD who are assessed to be candidates for revascularisation, the debate over PCI vs. surgical revascularisation has raged on for over 2 decades. To date, all major studies evaluating PCI vs. CABG have been underpowered for the hardest of clinical endpoints, all-cause mortality. Despite this, coronary artery bypass grafting (CABG) has proven superior to PCI, particularly in terms of the need for revascularisation. In the era of current contemporary thin strut, -limus derivative drug eluting stents this gap has however begun to narrow. The left internal mammary artery (LIMA), resistant to atherosclerosis and providing 15 year patency rates in excess of 95% is a hard target for any DES to match up to. Attempts to achieve an improved outcome in mortality in patients selected to undergo surgical revascularisation have fallen short. Despite the high attrition rate of saphenous venous bypass grafts (SVBGs), complete arterial revascularisation with bilateral internal mammary grafts,[11] or alternatively a LIMA + radial artery conduit[6] vs. LIMA + SVBG, have not positively impacted on mortality. The LIMA is clearly the key to favourable outcomes with CABG, supporting the contemporary surgical technique.

SYNTAX, FREEDOM and BARI-2D have all provided guidance in terms of the long-term benefits of CABG over PCI in the revascularisation of MVD. To their credit they have recently been backed up by the first pooled analysis of patient-level data adequately powered for all-cause mortality and sub-group analysis.[4] In the overall cohort with MVD and/or left main disease

(LMD), 5-year mortality was significantly lower after CABG than after PCI. The main advantage of CABG is provided from 4 years onwards. In those with MVD and diabetes, CABG outclassed PCI regardless of the complexity of coronary anatomy. Similar to SYNTAX however, PCI was found to be non-inferior to CABG in non-diabetics with low anatomical complexity. Interestingly, in the sub-group analysis of LMD, PCI was non-inferior to CABG regardless of anatomical complexity or diabetes status. This finding supports currently available evidence out to 3 years from EXCEL, that PCI is non-inferior to CABG in LMD of low-to-intermediate angiographic complexity.

This pooled analysis of 11 RCTs provides an important contribution to our understanding of the best choice of revascularisation strategy for patients with MVD.[4] In patients who are both clinically and angiographically suitable for PCI or CABG, diabetes is an important treatment modifier. In diabetics CABG is the clear choice, regardless of SYNTAX score.

In conclusion, PCI does provide patient reported symptom relief compared to placebo + OMT in patients with single-vessel stable CAD who fail medical therapy. Although the data is not quite there yet, it is highly probable that we are headed for a change in practice where FFR-guided PCI will become a requirement before stent implantation in stable CAD. This would not be unreasonable given the proven inaccuracy of our visual angiographic assessment of intermediate lesion severity, and the potential to influence hard clinical endpoints. It is unlikely that more robust data evaluating revascularisation strategies for stable MVD will become available anytime soon.[12] Therefore, for diabetics with MVD, regardless of anatomical complexity, CABG is the clear choice. For those with MVD of low anatomical complexity either PCI or CABG is an option, dependent on operator ability, and, most importantly informed patient choice.

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