openheart

Why percutaneous revascularisation might not reduce the risk of myocardial infarction and mortality in patients with stable CAD?

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To cite: Benenati S, De Maria GL, Kotronias R, *et al*. Why percutaneous revascularisation might not reduce the risk of myocardial infarction and mortality in patients with stable CAD?. *Open Heart* 2023;**10**:e002343. doi:10.1136/openhrt-2023-002343

Received 1 May 2023
Accepted 7 August 2023

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ABSTRACT

Percutaneous coronary intervention (PCI) is widely adopted to treat chronic coronary artery disease. Numerous randomised trials have been conducted to test whether PCI may provide any prognostic advantage over oral medical therapy (OMT) alone, without definitive results. This has maintained the paradigm of OMT as the first-line standard of care for patients, reserving PCI for symptom control. In this review, we discuss the current evidence in favour and against PCI in stable coronary syndromes and highlight the pitfalls of the available studies. We offer a critical appraisal of the possible reasons why the existing data does not provide evidence supporting the role of PCI in improving clinical outcomes in patients with stable coronary syndromes.

INTRODUCTION

Whether percutaneous coronary intervention (PCI) improves the prognosis of most patients with stable coronary syndromes has been debated for many years. Predictably, PCI techniques have continued to evolve but hard randomised trial evidence that undertaking PCI improves prognosis in patients without obstructive left main stem (LMS) disease has not been forthcoming. Consequently, optimal medical therapy (OMT) is considered as the first choice for most stable patients and revascularisation is only considered after OMT failure and used for symptom control.[1]

In real-world practice, enthusiastic interventional cardiologists find this relegation of the role of PCI to a second-line therapy a cause of frustration and confusion. This uncertainty arises from the interventional 'mantra' that ischaemia is the principal adverse pathophysiological process in patients with coronary disease and that PCI effectively abolishes ischaemia. Consequently, it has been assumed by interventionalists that PCI and ischaemia abolition should be beneficial for patients even in the absence of symptoms and that undertaking PCI should benefit long-term prognosis. Here, we will discuss the contemporary evidence about the impact of PCI in patients with stable presentation, and provide an overview of possible factors that could be considered when contemplating PCI in practice and future studies.

Contemporary evidence of PCI versus OMT in patients without LMS/LMS-equivalent disease: an overview

Several studies designed to assess the prognostic benefit of both angio-guided[2 3] and fractional flow reserve (FFR)-guided[4] PCI over OMT have not shown reduction in myocardial infarction (MI) or death in the invasive arm. The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) study[5] was conceived to overcome the limitation of these previous protocols, avoiding the influence of individual physician's judgement and providing a large and adequately powered trial to specifically compare an initial invasive approach or OMT in symptomatic patients.

There are a number of caveats to consider when adding the results of the ISCHEMIA into our discussion. In the ISCHEMIA trial, PCI accounted for roughly three out of four revascularisations in the invasive arm, whereas the remaining patients were treated with coronary artery bypass graft (CABG). Therefore, it is not correct to interpret the outcomes of the invasive approach as if it exclusively included percutaneous revascularisations. CABG is more beneficial than PCI in patients with left main disease and three vessel disease with extensive atherosclerotic burden, notably these populations were excluded from the ISCHEMIA trial. Moreover, CABG increases the risk of adverse events compared with PCI in the short term,

whereas its benefit is expected to manifest later. In other words, it is probably speculative to expect that a benefit of the invasive arm (if any) could be driven by CABG in a chronic and anatomically low-risk population such as that enrolled in the ISCHEMIA. On the other hand, there is solid evidence of the downsides of surgery, as opposed to PCI, in the early phase after revascularisation, which could have played a major role in driving the trial results against the invasive arm. In light of these considerations and considering the low number of patients treated with surgery, we will hereinafter discuss about the ISCHEMIA as a study of PCI versus OMT, expanding on the possible influence of CABG on the study results when deemed necessary. Although the initial data showed no difference between revascularisation and OMT,[5] recently published data,[6] at a median follow-up of 5.7 years, suggests a lower cardiovascular mortality in the invasive arm (adjusted HR 0.78, 95% CI 0.63 to 0.98). This, surprisingly, at the expense of of a 44% increase in non-cardiovascular mortality, leading to neutral results on overall mortality. Notably, although initial follow-up events were adjudicated, subsequent events in the 'extended' phase were not and non-fatal events such as MI and stroke were not collected.[6] Together with the lack of central adjudication for the cause of deaths that occurred during the extended follow-up phase, this suggests we should interpret the study results with caution.[6]

Aiming at reconciling the discrepancies between previous studies and increasing the statistical power of available estimates, a number of meta-analyses have been performed.[7–12] Pooling 14 trials and nearly 15 000 patients, Bangalore *et al*[7] showed no difference in terms of survival and MI, although the latter finding resulted from a reduced risk of spontaneous MI in the face of higher frequency of periprocedural events. Soares *et al*[10] showed benefit of CABG (but not PCI) on MI, with no benefit of revascularisation on mortality, and this was confirmed by a Bayesian meta-analysis from Kumar *et al*.[8] In contrast, Navarese *et al*[9] found lower cardiac death in the revascularisation arm but of note, at meta-regression, the prognostic benefit of revascularisation was linearly correlated with follow-up length, but also with the prevalence of three-vessel disease, supporting the hypothesis that survival benefit may be more evident in patients with an extensive burden of disease, in whom CABG (rather than PCI) may be more effective in reducing both spontaneous MI and mortality in the long-term. Notably, a broad proportion of studies included by Navarese *et al* enrolled CABG-treated patients, with CABG being the only strategy tested against OMT in a significant proportion of cases. Furthermore, many studies dated back to a non-contemporary medical therapy era, which could emphasise the advantage of revascularisation compared with other meta-analyses including fewer (but more contemporary) studies.[13] Of note, however, in the FAME 3 study FFR-guided PCI did not reach the non-inferiority compared with CABG in patients with three vessel disease, suggesting that, in patients with high atherosclerotic burden, even pursuing a contemporary physiology-guided approach may not be as beneficial as CABG.[14]

Most recently, the REVIVED-BCIS2 trial has shown no impact from PCI on clinical outcomes (and left ventricular ejection fraction) in 700 patients with heart failure and reduced ejection fraction, despite the coexistence of 'extensive' coronary artery disease (CAD) (mean British Cardiovascular Intervention Society jeopardy score 9.3) and proven myocardial viability.[15]

Why cannot PCI improve hard outcomes? A point-by-point critical appraisal

Potential pitfalls of currently available randomised controlled trials (RCTs) are shown in the figure 1 and, thereafter, discussed in a point-by-point approach.

'Barking up the wrong tree'? Considerations on myocardial ischaemia

Most studies discussed so far compared PCI and OMT on a background of established myocardial ischaemia. The fundamentals of such an approach are explained by the dose–response association between ischaemia and outcomes, with the former being almost linearly associated with overall mortality risk when involving more than the 10%–15% of the myocardial mass.[16 17] Hence, reducing the extent of myocardial ischaemia should reduce adverse events. Even though broadly correct, this line of reasoning has its limitations.[17]

The first demonstration that extent of ischaemia could justify the use of revascularisation over OMT was provided by Hachamovitch *et al*,[16] who showed a significant advantage of the former (either PCI or CABG, which were almost equally represented in the study population) when the ischaemic tissue exceeded the ≈ 10% of the myocardium. In the attempt to replicate the results of this retrospective study, a subanalysis of the COURAGE trial was also performed.[18] Disappointingly, this showed no benefit of PCI in patients with moderate-to-severe ischaemia in the adjusted analysis, and thus it failed to confirm the earlier results. Furthermore, in a larger (N=1505) subanalysis of the BARI-2D trial, MI and death were successfully predicted by the amount of scarred, rather than ischaemic, myocardium.[18] Later, in a substudy of the STICH trial, Panza *et al* could not find any significant association between myocardial ischaemia and cardiovascular mortality also in patients with CAD with left ventricular dysfunction.[19] Lastly, a subanalysis of the ISCHEMIA trial was also conducted,[20] analysing data from 5105 (99%) patients of the original ISCHEMIA population, in whom ischaemia severity was adjudicated through a core-lab analysis. Among the study outcomes, moderate-to-severe ischaemia was only associated with MI, but this relationship was lost after adjusting for CAD burden. Notably, CAD burden was strongly associated with most of trial endpoints. Furthermore, in the subgroup with the most severe CAD, PCI reduced the 4-year rate of the composite of cardiovascular death or MI. Shedding further light on the key importance of plaque burden, a

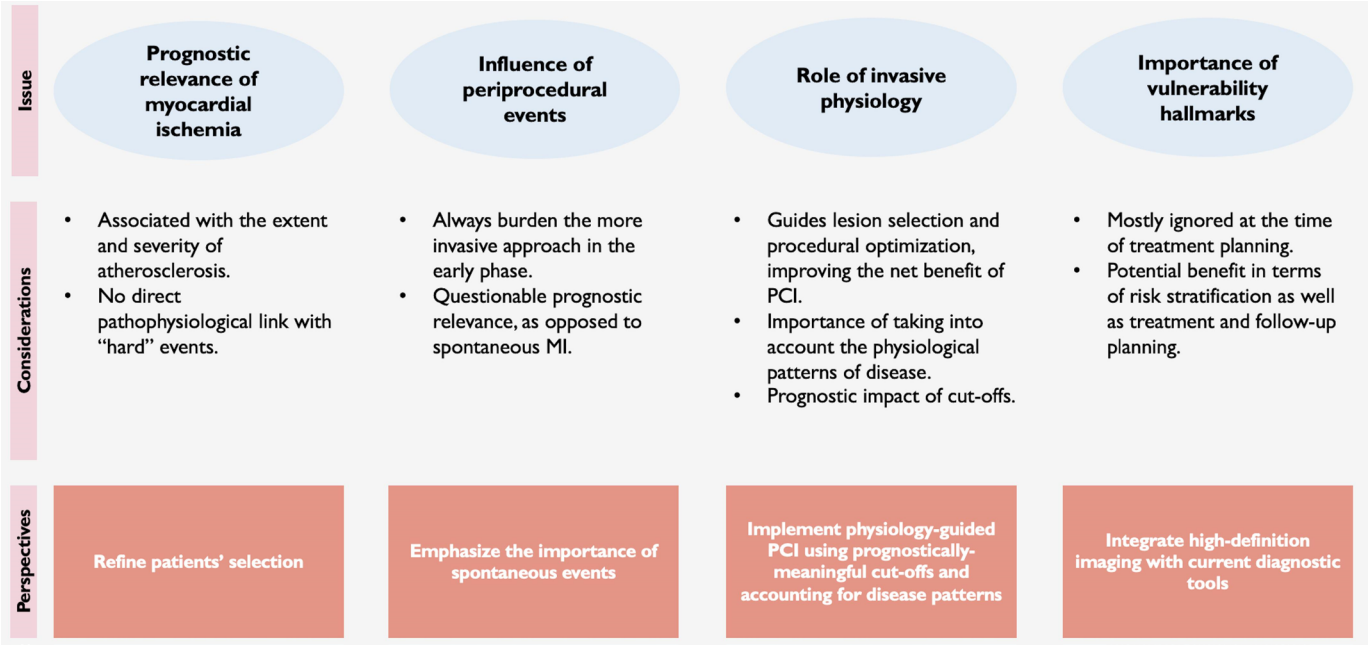

Figure 1 Why cannot we prove that PCI improves outcomes in stable CAD? CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

recent study by Noguchi *et al*, showed a significant association between the former and long-term survival in patients with LMS disease, irrespective of minimal lumen area.[21] Despite these data using non-invasive ischaemia assessment, there are no clues that invasive physiology might modify this relationship.

The pathophysiological link between myocardial ischaemia and hard clinical outcomes is probably not straightforward. It has been described that acute plaque destabilisation resulting in MI and cardiac death is mostly caused by abrupt plaque rupture or erosion, a phenomenon profoundly related with plaque morphology. Although this often occurs in severely stenotic plaques, previous natural history studies have shown that even mild lesions, most often not prone to produce ischaemia, can result in plaque instability and coronary thrombosis.[22] A recent study by Prati *et al* showed a significant risk excess of hard events (cardiac death and target-vessel MI) in patients with optical coherence tomography (OCT)-defined high-risk plaque features observed in otherwise angiographically non-significant (<50%) stenoses involving the proximal LAD.[23] While myocardial ischaemia mostly depends on the flow-limiting nature of a stenosis, the occurrence of clinical events is not strictly related with the latter, being instead associated more with plaques features including lipid content, fibrous cap thickness and inflammation.[23] These data contribute to the explanation of these observations. First, addressing a single ischaemia-causing lesion—which is the usual approach with PCI—may effectively reduce ischaemia, but not necessarily prevent adverse events related with distant lesions not causing ischaemia at the time of PCI. These bystander plaques may still subsequently present with features making them prone to 'instability' and consequently, a less 'localised' approach could be preferrable. For instance, OMT can blunt (or even revert) atherosclerosis progression and plaque vulnerability, with its benefit extending far beyond single lesions and treat the whole coronary tree.[24] Second, among revascularisation techniques, CABG provides protection to the most proximal segments and most often allows complete revascularisation to be achieved, which potentially justifies its benefit over OMT and PCI, especially in cases of extensive disease.[9 25]

Are we choosing the right endpoints? Considerations on periprocedural events

Among the hypotheses put forward to explain the results of the ISCHEMIA trial[26–28] and other RCTs showing the neutral effect of revascularisation (especially PCI), the impact and weight of periprocedural adverse events is important.

In the ISCHEMIA trial, PCI benefit was clearly outweighed by OMT in the first months, whereas a steeper accrual of event rate in the conservative arm was observed thereafter, mirrored by the fact that the OMT hazard curve crossed the invasive treatment curve at approximately 2 years. As we learnt from previous studies comparing treatments with different profiles of invasiveness,[29] the higher invasive nature inherent with PCI (compared with OMT)—brings a consequent heightened risk of short-term complications. According to an analysis by Chaitman *et al*,[30] periprocedural MI was the uppermost contributor for the early disadvantage of PCI in the ISCHEMIA study, whereas spontaneous events were definitely more frequent in the conservative counterpart, especially in the mid-term to long term. The impact of procedural MI is debated extensively but it is clear that

only large events have clinical relevance, whereas most events do not have any relevant effect on prognosis,[31 32] as opposed to type 1 MI.[30] Interestingly, this ISCHAEMIA subanalysis showed a prominent impact of periprocedural MI definition on the primary endpoint, with the invasive arm impacted by a more 'inclusive' definition, which resulted in a significant difference in favour of OMT.[30]

In summary, when analysing the ISCHEMIA results, we should be aware that (1) the neutral result of the comparison between PCI and OMT are influenced by an inherent drawback of PCI, namely periprocedural MI, whose impact on long-term prognosis is questionable and (2) that at a later stage (but not too late, as curves cross within 2 years) during follow-up, the early avoidance of possibly prognostically less relevant events (namely periprocedural MI) in patients treated with OMT sustained a risk excess in terms of spontaneous MI. By extending these results to the whole spectrum of modern RCTs comparing PCI and OMT, a recent meta-analysis showed an advantage of PCI when periprocedural events were excluded from the primary endpoint.[12]

Are we stenting the right lesion? Considerations on coronary physiology guidance

Absence of physiological guidance

Another relevant issue shared by most RCT of PCI vs OMT is the absence of invasive physiology assessment in the PCI arm. Since the publication of pivotal RCTs,[4] intracoronary physiology has become the gold standard to guide coronary revascularisation. Indeed, current international guidelines strongly support the use of FFR and instantaneous wave-free ratio (iFR) for this purpose.[33 34] Whether a physiology-guided approach could have improved PCI outcomes, particularly in terms of 'hard' events such as spontaneous MI or death, is uncertain. So far, evidence in this direction is lacking with most benefits of intracoronary physiology being actually driven by a reduction of repeat revascularisation.[4 11] However, large real-world studies have claimed an improvement of survival after FFR-guided PCI, as compared with angio-guided PCI,[35] as well as lower number of lesions treated and lower number of stents implanted when treatment is guided by invasive coronary physiology.[36]

Furthermore, intracoronary physiology improves the identification of CAD patterns (ie, focal, mixed or diffuse), as compared with angiography alone.[37 38] Although outcome data are currently lacking in this regard, preliminary data suggest that PCI results may be suboptimal in non-focal disease.[37 39] Implementing physiology-guided PCI may hence help tailoring the revascularisation strategy, avoiding unsuccessful PCI and the associated risk of periprocedural events. Not least, intracoronary physiology allows optimising PCI results, which could further reduce the likelihood of adverse events. Transposing these potential advantages to the ISCHEMIA and other RCTs not adopting invasive physiology is not possible. However, one could speculate a potential reduction of unnecessary PCI, resulting in a lower rate of procedure-related complications and, in turn, a larger net benefit in patients who could have actually benefited from an invasive approach.

The choice of physiological cut-offs

Since the publication of the FAME 2 trial,[4] the scientific community has accepted to dichotomise the treatment of stable CAD according to a 0.80 FFR cut-off. This was thereafter adopted as a reference to test the non-inferiority of iFR and of other non-hyperaemic physiology indices[40] and this threshold has become a reference in international guidelines.[33] This was despite the original data provided by the Deferral Versus Performance of PTCA in Patients Without Documented Ischemia (DEFER) study,[41] in which a 0.75 cut-off was used. The latter was also the most commonly detected by previous studies validating FFR against non-invasive techniques for ischaemia detection.[42] A large patient-level meta-analysis by Johnson *et al* showed a gradual smoothening of major adverse events rates across progressively increasing FFR values, suggesting a continuous (rather than dichotomic) association between the latter and outcomes occurrence. Most importantly, however, the same study reported a benefit of FFR-guided PCI, as compared with OMT, only for values below 0.67.[43] A number of studies have compared the clinical outcomes of PCI and OMT in patients in the so-called 'grey zone', that is, FFR values between 0.75 and 0.80. A meta-analysis by Andreou *et al* pooled the results of 6 non-randomised studies including more than 2300 patients, showing no differences between PCI and OMT in stenosis within the FFR grey zone.[44] Thereafter, a small randomised trial has confirmed these results, although in a cohort of only 104 patients.[45] Importantly, a subanalysis from the DEFER trial showed that FFR measurement significantly loses accuracy within the grey zone (particularly when approximating 0.80) with concrete possibilities that FFR-based recommendation would change across repeat measurements obtained a few minutes apart.[46] Guidelines and consensuses endorse the 0.80 threshold but a cautious and critical approach when deciding about revascularising stenosis with an FFR between 0.75 and 0.80[34] should be re-evaluated.

The role of plaque morphology and patients' vulnerability

There are data questioning the reliability of coronary physiology in specific subsets of patients with stable CAD.[34] Among them, patients with diabetes mellitus (DM) are the most representative group. The limited reliability of invasive coronary physiology in patients with diabetes is well known from previous literature. Previous studies have shown that, in patients with DM, non-haemodynamically significant (FFR>0.80) stenoses have a relevant risk of future cardiac events.[47] In a study by Liu *et al*, a negative FFR was not able to stratify the risk of subsequent cardiovascular events in DM, as opposed to patients without DM. When including only patients with FFR values >0.85, the same study found a more than

twofold higher risk of the composite of death and MI in the DM arm.[48] More recently, the COMBINE OCT-FFR study included patients with DM with any indication for coronary angiography and at least one intermediate (≥40% to ≤80% diameter) coronary stenosis. Among FFR-negative stenoses, the study demonstrated a strikingly higher risk of the primary endpoint (a composite of cardiac death, target-vessel related MI) in the presence of thin cap fibro-atheroma (TCFA) vs non-TCFA lesions. Conversely, non-revascularised non-TCFA FFR-negative lesions led to similar rates of events as compared with revascularised FFR-positive stenoses.[49]

Whether special attention could be required in additional scenarios to patients with DM is not conclusively established. However, we probably should take into account certain subgroups, such as patients with recent (<30 days) ACS, who have been mostly excluded by RCTs of PCI versus OMT.[2–5] In this regard, it should be noted that multivessel PCI of angiographically significant lesions proved to be superior compared with medical therapy after STEMI in the COMPLETE trial,[50] probably driven by the high vulnerability profile of bystander disease in this population.[51] It is in fact not surprising that, later, FFR failed to reach superiority over angiography to guide complete revascularisation in the same population,[52] with clues that a risk excess driven by FFR-negative lesions might have substantially contributed to dissipate its advantages.[53] This is also consistent with the findings of seminal studies such as the PROSPECT and PROSPECT II. Analysing large cohorts of patients with recent MI, both these studies showed plaque morphology to be strongly associated with future adverse events, mainly recurrent spontaneous MI and unstable angina.[22 54] Of note, a subanalysis of the PROSPECT study also investigated the interaction between DM and plaque morphology after an ACS, showing that DM patients without TCFAs have similar prognosis compared with non-DM patients.[55] This supports the prominent role of plaque characterisation beyond clinical risk stratification according to DM status.

As current guidelines acknowledge,[56] atherosclerotic disease is progressive and subject to relapses of plaques instability, potentially—yet not necessarily—leading to ACS.[57] It is reasonable to assume that some patients may have heightened plaque vulnerability and be more prone to abrupt disease instability and MI development.[58] As for non-invasive ischaemia tests, invasive coronary physiology may also fail to effectively stratify the risk of events associated with highly vulnerable but non-haemodynamically significant lesions, whereas intracoronary imaging could potentially be more reliable. However, the assumption that revascularisation and preventative stenting would be the correct answer is probably misleading and we should remind ourselves that current risk stratification is not exempt from pitfalls.

CONCLUSIONS

The more effective we are at stabilising CAD, the more demanding the challenge will become to demonstrate the risk–benefit ratio of invasive treatments. The currently available RCTs, mostly conceptualised to target ischaemia, do not prove a definite advantage of PCI over OMT alone, at least in terms of 'hard' clinical outcomes. Based on this realisation, PCI should only be used to reduce symptoms in most cases. In the future, accounting for plaque morphology and patients vulnerability could probably change this scenario, also allowing the interventional community to move beyond what we consider a 'disappointing' result for PCI and acknowledging reasons for this observation. This reconsideration will allow critical reappraisal of specific aspects of our practice and improved outcomes for our patients.

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Contributors SB and GLDM conceived the study and drafted the first manuscript; GLDM, RK, IP and APB reviewed the initial draft. All the authors approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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