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Clinical application of results of the ISCHEMIA trial

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ABSTRACT

More than a decade after the Clinical Outcomes Utilising Revascularization and Aggressive Drug Evaluation (COURAGE) trial, International Study of Comparative Health Effectiveness With Medical And Invasive Approaches (ISCHEMIA) is the second large clinical trial to challenge the concept of revascularization in chronic coronary syndromes whilst addressing some of the shortfalls of its predecessor.

Design of ISCHEMIA

ISCHEMIA trial is a large prospective multicentre randomised controlled trial that aims to establish the preferred treatment strategy for patients with chronic coronary syndrome (CCS) and moderate to severe reversible myocardial ischemia, proven by a non-invasive functional test. The study compared optimal medical therapy alone versus an invasive strategy, incorporating invasive coronary angiography and revascularization - if indicated – combined with optimal medical therapy. [1] The trial only enrolled patients with inducible myocardial ischemia, as proven by a non-invasive functional assessment modality that could either be exercise tolerance testing, stress echocardiography, stress perfusion cardiac magnetic resonance imaging and nuclear imaging. Provisionally, over 26.000 screened patients at the recruiting sites were identified with moderate to severe inducible ischemia. However, this was reduced to a total of 8518 following the application of the trial's exclusion criteria that included patients with severe angina, reduced left ventricular systolic function, recent acute coronary syndromes, symptomatic heart failure or impaired renal function. At this stage, a computed tomography coronary angiography (CTCA) was utilised prior to randomization to exclude patients with significant left main disease, as well as patients with normal or non-obstructive coronary disease. Its findings were blinded for the investigators to eliminate potential operator selection bias.

A total of 5179 patients were randomized either to a conservative approach or to an invasive strategy. Importantly, invasive physiologic assessment with fractional flow reserve (FFR) or with instantaneous wave free ratio (iFR) was limited to patients within the invasive group with lesions where non-invasive ischemia testing was discrepant with the angiographic finding: either angiographically mild lesion despite non-invasively shown ischemia, or angiographically tight stenosis despite no perfusion defect. If confirmed and being indicated, revascularization would be performed either by percutaneous coronary intervention (PCI) using drug-eluting stent or by coronary artery bypass surgery (CABG) (**Fig. 1**). Overall, no more than 20% of patients within the invasive arm underwent either FFR or iFR [1].

Hard endpoints included death and myocardial infarction (MI) with expanded composite primary endpoints including MI, cardiovascular death, hospitalization for unstable angina or heart failure and cardiac arrest resuscitation with an overall median follow-up duration of 3.2 years.

Results of ISCHEMIA

Results of the trial suggest that chronic coronary syndromes should be treated with OMT alone as, statistically, there were no significant differences detected in cumulative event rates between both strategies up to 5 years follow-up (invasive group: 16.4% vs OMT only group: 18.2%; hazard ratio 0.93; 95% confidence interval [CI] 0.80-1.08) providing significant unprotected left main stem and severe angina are excluded. Furthermore, it demonstrates a statistically relevant set of data that infers no overall all-cause mortality benefit of an invasive strategy compared to that of a conservative approach (Invasive group: 9% vs OMT only group: 8.3% hazard ratio, 1.05; 95% CI, 0.83 to 1.32) [2]. Just over 20% of those in the invasive arm did not undergo revascularization and 21% of those in the conservative arm did undergo revascularization - 15% did so before a primary outcome was achieved.

An additional aim of the trial was to assess angina related functional status in both groups [3], a total of 4617 enrolees were

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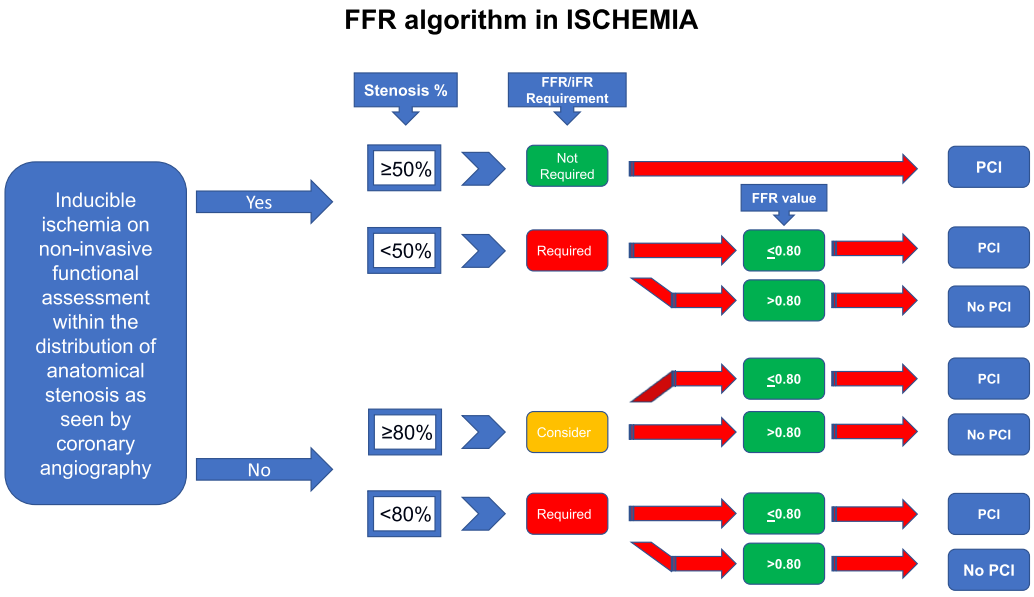

Fig. 1. FFR algorithm in ISCHEMIA

deemed eligible for quality of life analysis across both cohorts. Overall, there was a marginal advantage of an invasive strategy on improving quality of life scores which was measured using the Seattle Angina Questionnaire (SAQ); however, when only comparing those with daily or weekly angina there is a significant difference with 50% of these patients being angina free at one year as compared to around 30% in the OMT only group. Overall, patients in the invasive cohort, providing they have frequent angina, are 3 times more likely to experience a better quality of life than their conservative group counterpart [3].

ISCHEMIA versus clinical reality of patients with CCS

As mentioned, findings suggest there is no statistically relevant difference between a conservative approach versus an invasive strategy in terms of the combined endpoint of cardiovascular death, myocardial infarction, hospitalisation for unstable angina or heart failure and resuscitation for cardiac arrest for patients with CCS and moderate to severe myocardial ischemia [2].

While the findings definitely shed new light on the indications of revascularization in CCS, the limitations of the trial also have to be considered. Obviously, with respect to the exclusion of patients with 'highly symptomatic' angina, the findings are not relevant for a marked portion of the typical population cohort, undergoing an invasive work-up and eventual revascularization especially when considering other exclusion criteria within the trial. This resulted in a highly selective patient cohort as compared to a typical all comer population and should be considered when attempting to interpret and implement such results in daily clinical practice. It is worth noting that randomisation in the trial occurred in less than 20% of all patients across all sites who were initially identified as having moderate to severe inducible ischaemia. In fact, a subsequent prospective registry trial suggests that only around 4% of patients in a contemporary real-world cohort of patients with CCS would be eligible for enrolment and randomisation in ISCHEMIA. [4]

Including patients only with non-invasively proven moderate to severe myocardial ischemia, the inclusion of revascularisation by means of CABG, only utilising latest generation drug eluting stents and anatomical results of the CTCA being blinded to the investigators are all important assets of the ISCHEMIA trial. However, regarding non-invasively proven myocardial ischaemia, protocol allowed various modalities for non-invasive assessments of myocardial ischemia, including exercise tolerance testing, stress echocardiography, stress perfusion cardiac magnetic resonance imaging and nuclear imaging. This has clearly led to certain heterogeneity in the accuracy of the diagnostic work-up. Additionally, the exclusion of recent ACS patients may have also had an impact on negatively impacting the invasive cohort of the trial given the findings of the COMPLETE trial demonstrating that complete revascularisation and not just culprit lesion PCI in STEMI patients had a positive impact in reducing cardiovascular death, MIs or ischaemia driven revascularisation [5].

As mentioned, one of the important assets of ISCHEMIA is the inclusion of CABG as a means of revascularisation and therefore, addressing one of the shortfalls of its predecessor (COURAGE). CABG is an important and a recommended option for revascularisation in patients with a higher degree of complex multivessel disease due to improved outcomes when compared to PCI as evidenced historically by the largest randomised controlled studies comparing both strategies [6,7], though it is important to remember that ISCHEMIA did (understandably) exclude those with left main stem disease which represents an important cohort of CCS patients that get referred for CABG.

From a historic perspective, reversing myocardial ischaemia has been deemed imperative which is why it had been important to identify [8] and on this basis methods were conceptualised and refined based on the notion of identifying ischaemia more specifically at a lesion level resulting in the development of pressure wire studies with the fractional flow reserve being the first to be validated as a proxy to identifying vessel- or lesion specific inducible ischemia [9] and later proven to be beneficial with a predictive value and utility in guiding PCI in CCS. [10–12]. Nevertheless, in ISCHEMIA, guidance for revascularization itself was designed mainly based on the results of the non-invasive testing. Therefore, its appropriateness can also be markedly influenced by means of the chosen non-invasive test modality, having the risk of potential over- or undertreatment of potential 'PCI worthy' lesions without invasive vessel level functional guidance.

Even though MI incidence within the two groups of ISCHEMIA was similar statistically when using the prespecified two MI definitions in the trial, there is evidence that the chosen definition of MI in ISCHEMIA does have an impact on management and prognosis and therefore when using the designated primary and sec-

ondary definitions in type 1 MI events in the 5-year follow-up of ISCHEMIA patients, MI events were more frequent within a conservative strategy and statistically significant [13]. From an angina control perspective within the ISCHEMIA trial, around one third of all patients enrolled in both the invasive and conservative cohorts had no angina at all (34.3% in the invasive group vs 36.6% in the conservative group) with only 2% of patients reporting daily angina and about 20% reporting weekly angina. In fact, over two thirds of randomised patients reported either monthly angina or no angina at all [3] – this contravenes the typical patient seen in this cohort of the population.

ISCHEMIA and how it compares to previous landmark trials

Identification of inducible ischaemia in guiding revascularization and PCI in chronic coronary syndromes at the vascular/lesion level is important, and to understand why, it would be essential to revisit the landmark trials of FFR: Deferral versus Performance of Percutaneous Transluminal Coronary Angioplasty in Patients Without Documented Ischemia (DEFER), Fractional Flow Reserve versus Angiography for Percutaneous Coronary Intervention (FAME) and Fractional Flow Reserve Guided PCI versus Medical Therapy in Stable Coronary Disease (FAME2).

DEFER is a prospective multicentre randomised controlled trial in which patients with angiographically significant but functionally non-significant lesions (FFR>0.75) were randomly assigned to either a PCI performance group or a conservative approach - the deferral group. The reference group constituted those patients with at least one lesion which is both anatomically significant as well as functionally significant as proven by FFR (FFR value <0.75). The trial demonstrated no significant difference in event free survival from the composite endpoint of acute spontaneous MI, and death between the two groups (deferral group 89% vs performance group 83%; p=0.27) in fact the composite endpoint of spontaneous MI and death was higher in the performance group at the 5 year follow up of the DEFER trial [10] and also maintained such results at the 15 year follow up in which 93% of all randomised patients were identified, and even at this late stage there was no statistically relevant difference between the two cohorts of defer group versus performance group when it comes to mortality rate (33% vs. 31.3%, respectively; p=0.79) [14]

The FAME trial on the other-hand is a prospective multicentre randomised controlled study and enrolled 1005 patients with multi vessel coronary artery disease across 20 medical centres in Europe and the United States. This trial aimed to compare the outcomes of angiography guided PCI in chronic coronary syndromes versus FFR guided PCI and therefore Patients assigned to angiography guided PCI underwent stenting of all indicated lesions, whereas those assigned to FFR guided PCI underwent stenting of indicated lesions only if the FFR value was 0.80 or less. Primary endpoints included a composite of death, MI and repeat revascularization. The results demonstrated a significant risk reduction in the rate of composite end points at 1 year for FFR group (13.2% vs 18.3% p= 0.02) with benefit being maintained up to 2 years [15]. However, there was a similar rate of progression in the two arms between 2 and 5 years and at 5 years major adverse cardiac events occurred in 28% of the FFR group and 31% in the angiography guided group (p=0.31) [16]

FAME2 is also a prospective multicentre randomised controlled trial and is the only trial so far in which there is a head to head direct comparison between an invasive strategy utilising percutaneous intervention (PCI) as a means of achieving revascularization and directed only in lesions which had been proven to be ischaemia inducing on FFR combined with OMT versus OMT alone in lesions that again, had been proven by FFR to be ischaemia inducing at lesion level. (**Fig. 2**; **Table 1**) Overall, 1220 patients were enrolled and 888 randomised, primary endpoints included death, MI and urgent revascularization (defined as those undergoing PCI before discharge on a subsequent admission), FFR cut-off was 0.8 and only drug eluting stents were used. Recruitment was halted prematurely after enrolment of 1220 patients by the health and safety committee with follow up being cut from 2 years to just 7 months due to a highly statistically relevant difference within the two arms [12]. This trial demonstrated that PCI + OMT group had a significantly lower event rate of the primary endpoint as compared to those receiving OMT alone (4.3% vs 12.7%, respectively; p= <0.001). What is interesting is that the incidence of the primary endpoint after targeted PCI to only ischemia inducing lesions as proven by FFR with the latest generation drug eluting stent was the same as the reference group who had no ischaemia inducing lesions, again, as proven by FFR [12]. At 5 years, the rate of the primary end point was lower in the PCI group than in the medical-therapy group (13.9% vs. 27.0%; hazard ratio, 0.46; 95% confidence interval [CI], 0.34 to 0.63; P<0.001). However, the difference was mainly driven by urgent revascularizations, which occurred in 6.3% of the patients in the PCI group as compared with 21.1% of those in the medical-therapy group (hazard ratio, 0.27; 95% CI, 0.18 to 0.41). There were no significant differences between the PCI group and the medical-therapy group in the rates of death. No significant difference in the rate of the primary end point between the PCI group and the registry cohort. The majority of urgent revascularizations were triggered by worsening angina, ischemic changes observed on electrocardiography, or myocardial infarction. By the 5 years mark, 225 patients (51.0%) who had originally been assigned to receive medical therapy alone had undergone revascularization [17]. Given the high rate of crossover to PCI among patients who had been originally assigned to medical therapy, an intention-to-treat analysis may have underestimated the potential benefit of PCI in regards to death, myocardial infarction, and severity of angina [17]. Contrarily, although this trial was a positive study for coronary revascularization by PCI in patients with CCS, whether urgent revascularization should be considered as a “hard outcome” has been a matter of debate. Clinical benefits from revascularization are therefore still questionable to improve the CCS prognosis.

These three landmark FFR trials collectively demonstrate a clear utility for FFR in guiding PCI decisions in CCS and are based on the concept of an implied benefit from reversing proven inducible myocardial ischemia by means of revascularisation and vice versa which, historically, trials such as that concluded by Hachamovic et al advocates [8]. However, results of ISCHEMIA and COURAGE trials directly contradict this concept and suggest a completely opposite outcome to FAME2 or indeed the meta-analysis of the three available randomized control trials of FFR guided PCI versus medical therapy concluded by Zimmermann et al that suggests favourable outcomes in hard endpoints and overall affirming the need for revascularization in stable coronary artery disease providing these are ischaemia inducing lesions [18]. DEFER and FAME on the other-hand strongly suggest that negative FFR lesions should be left alone - though it must be emphasised that FAME and DEFER trials are not designed to compare optimal medical therapy versus an interventional strategy.

There are multiple factors at play here leading to what may ‘appear’ to be contradictory results, this likely includes: anatomical considerations when attempting PCI in chronic coronary syndromes versus functional and haemodynamic relevance of such lesions, plaque vulnerability modification with adequate preventative pharmacological therapy versus degree of plaque stenosis and definitions of myocardial infarction with spontaneous versus periprocedural infarcts. Additionally, there is the reliability of subjective reporting of angina pectoris as a means of guiding PCI in chronic coronary syndromes over functional guidance and the placebo effects of PCI as demonstrated in the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in sta-

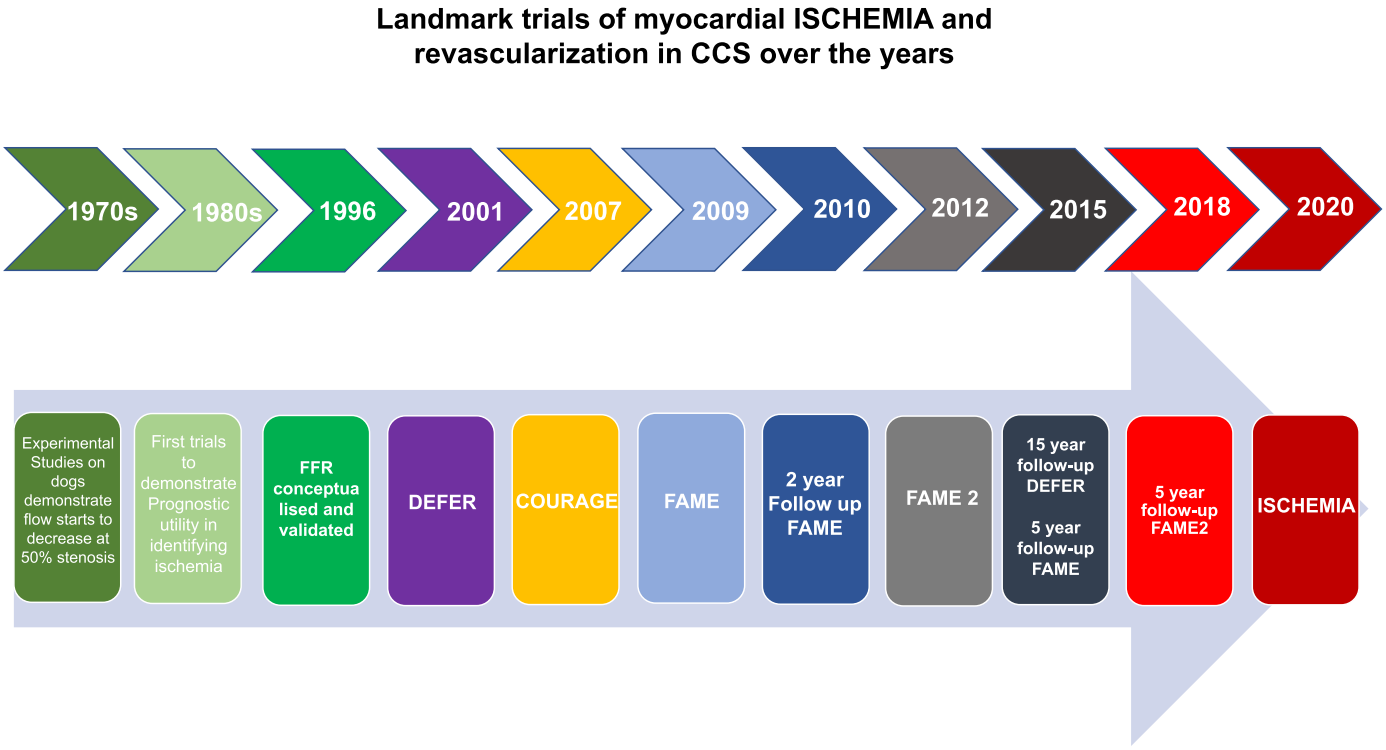

Fig. 2. Landmark trials of myocardial ISCHEMIA and revascularization in CCS over the years

Table 1
Landmark FFR studies vs. COURAGE and the ISCHEMIA trial

TRIAL	DEFER	FAME	FAME2	COURAGE	ISCHEMIA
Enrolled Patients	325	1905	1220	2287	8518
Randomized patients	325	1005	888	2287	5179
Publication year	2001	2009	2012	2007	2020
Design	Prospective MC RCT	Prospective MC RCT	Prospective MC RCT	Prospective MC RCT	Prospective MC RCT
Clinical question	Safety of deferring FFR negative lesions in CCS	Outcomes of FFR guided PCI vs. angio-only guided PCI in MVD in patients with CCS	Outcomes of FFR guided PCI+OMT vs. OMT alone in patients with CCS	Outcomes of PCI+OMT vs. OMT alone	Clinical outcomes on an invasive strategy+OMT vs. OMT alone in CCS
Pressure wire study	Yes (FFR)	Yes (FFR)	Yes (FFR)	No	Yes (FFR & iFR)
Composite primary endpoint	Death , MI, revascularization	Death, MI, revascularization	Death, MI, urgent revascularization	Death, MI	Death, MI, hospitalization for UA or HF and cardiac arrest resuscitation
Composite primary endpoint (%)	Deferral group: 17.8 Performance group: 29.2	Angiography group: 18.3 FFR group: 13.2	PCI+OMT: 4.3 OMT: 12.7	PCI group: 19 OMT group: 18.5	Invasive group: 16.4 OMT group: 18.2
Mortality (%)	Deferral group: 2.2 Performance group: 0.7	Angiography group: 3 FFR group:1.8	PCI+OMT group:0.2 OMT group:0.7	PCI group: 7.6 OMT group: 8.3	Invasive group: 9 * OMT group: 8.3
Revascularization	PCI	PCI	PCI	PCI	PCI or CABG
Drug eluting stents (%)	0	96.9	100	2.6	100

DEFER: Deferral versus Performance of Percutaneous Transluminal Coronary Angioplasty in Patients Without Documented Ischemia, *COURAGE:* The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation, *FAME:* Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention, *FAME2:* Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease, *ISCHEMIA:* International Study of Comparative Health Effectiveness With Medical and Invasive Approaches.
FFR: Fractional flow reserve, *PCI:* percutaneous intervention, *OMT:* optimal medical therapy, *iFR:* instantaneous wave-free ratio, *CCS:* chronic coronary syndrome, *MI:* myocardial infarction, *UA:* unstable angina, *HF:* heart failure, *MC:* multicenter, *RCT:* randomized control trial, *MVD:* multivessel disease
* Death from cardiovascular causes or myocardial infarction at 5 years

ble angina (ORBITA) trial, 2017 [19]. This was a double blinded multicentre trial at 5 centres across the UK, being designed to obtain objective evidence of symptomatic relief by adopting a placebo - controlled randomisation, through comparison between PCI versus placebo on relieving angina pectoris. Overall, 230 patients were enrolled with 200 undergoing randomisation (105 patients underwent PCI and 95 underwent a placebo procedure) and both groups underwent a medical optimisation phase over 6 weeks prior to their respective procedures – all patients had anatomically 'severe' single coronary artery stenosis (>70%) and all underwent a pressure wire study with either FFR or iFR (mean FFR: 0.69 and mean iFR: 0.76 – though around one third had a normal FFR or iFR). Primary endpoint included exercise time incrementation and the trial concluded there was no significant difference: (PCI minus Placebo 16.6 seconds or 28.4 seconds after PCI vs 11.8 seconds after OMT alone {placebo group}, 95% CI – 8.9 to 42.0 p=0.200) [19].

However, it could well be deduced that all of these trials do in fact carry a very clear unifying message, and that is to avoid an invasive strategy in CCS if possible as patients with stable coronary artery disease and chronic coronary syndromes who undergo an invasive strategy will always be exposed to a degree of risk incurred as a result of an invasive strategy. This could explain why both invasive and conservative groups in the ISCHEMIA trial had similar primary endpoints in the form of MI as the immediate procedural risk associated with an invasive strategy compares to a potentially protracted risk of a conservative approach, though both arms appear to be at cross roads at the 2.5-year point [2] and follow-up beyond 5 years may reveal the true and potentially different impact of both strategies especially given the fact that randomised patients to elective PCI in CCS plus optimal medical therapy appear to have reduced cardiac mortality with fewer spontaneous MIs when compared to an optimal medical strategy alone at longer follow-up times [20]. It is also clear from the findings of Hachamovic et al that outcomes are favourable if inducible myocardial ischaemia is reversed. Furthermore, the first of the landmark FFR trials to demonstrate a predictive value for FFR in guiding PCI: DEFER trial clearly proves even at the 15 year follow-up that FFR negative lesions are best left without revascularization and also infers that there is a considerable discrepancy between anatomical considerations of what is deemed a 'significant stenosis' on invasive coronary angiography and what is actually functionally relevant. This notion was further reinforced following the FAME trial, and as described above, demonstrated an advantage of FFR guided PCI over anatomical guidance and pure "eye balling" of lesions.

Aftermath of ISCHEMIA and impact on clinical practice

The ISCHEMIA trial is a large-scale study that is designed with one main objective, and that is to answer once and for all the question of whether reversing inducible ischaemia by means of revascularization in stable coronary artery disease is beneficial in terms of hard outcomes or even from an anginal symptom control perspective. Results suggest that the answer to this is no with limited benefit on symptoms. However, and as explained above, there are many caveats to consider within the trial when contemplating an OMT strategy alone and the implication this has on the clinical applicability of the trial to the relevant cohort with chronic coronary syndromes. However, what can be clearly extrapolated from ISCHEMIA and previous trials is that there is a relative risk associated with an invasive strategy compared to OMT alone and therefore decisions on such invasive strategies should be aimed only to those with 'PCI worthy lesions' with objective evidence of inducible ischaemia at lesion level as proven with a pressure wire study with either FFR or one of the non-hyperaemic indices.

An ideal trial, which may potentially be able to give more clarity regarding the question of whether revascularisation + OMT has an advantage over OMT alone in CCS should attempt to draw on, to a certain extent, the strengths of its predecessors and their limitations. It should incorporate a design ensuring a degree of uniformity and comparability in patient characteristics amongst both cohorts, especially in terms of the presence of anatomically flow limiting coronary atheroma, myocardial viability and the presence of inducible myocardial ischaemia in a significant territory of myocardium. Patients in both cohorts should have a similar baseline functional status with any limitation being attributed to angina and not due to other comorbidities; this could affirm a reasonably fair comparison between both strategies and it should also aim to be blinded to patients and recruiting physicians. To adopt this, the trial should therefore be double blinded and incorporate anatomical and functional investigative tools of myocardial ischaemia that is highly accurate with a good degree of specificity and sensitivity such as CTCA/CT-FFR (coronary computed tomography fractional flow reserve) and stress cardiac MRI (ideally maintaining homogeneity of a chosen non-invasive functional assessment) in the pre-randomisation phase. Positive results should then undergo lesion level assessments of myocardial ischaemia such as FFR to prove inducible ischaemia at the vascular level before randomisation - this will ensure appropriately guided revascularization within the invasive arm and comparability with similar lesions within the conservative arm. It should also be sufficiently powered in addition to rigorous follow-up to prove outcomes in hard end points and myocardial infarction. Revascularization options should include CABG in those with more complex multivessel disease with high SYNTAX scores as per ISCHEMIA trial.

Current guidelines are to a certain extent compatible with the above, only strongly advocating revascularization in those with objective evidence of inducible ischemia and failed medical treatment. Our diagnostic approach to patients with suspected CCS in light of ISCHEMIA could be summarised in the following: Firstly, the role of anatomical assessments as a key first step in assessment of patients with suspected CCS by means of CTCA or an invasive diagnostic coronary angiography remains key and reinforced by the trial; however, this should be followed by an invasive functional assessment if indicated. Secondly, even though results of ISCHEMIA would suggest avoiding revascularization in asymptomatic patients despite the presence of inducible ischemia detected non-invasively, invasive physiological assessments of myocardial ischaemia such as FFR and non-hyperaemic indices have been well validated with strong evidence supporting their utility in guiding PCI in CCS and therefore, could be regarded as gatekeepers to PCI in stable coronary artery disease especially in questionable cases [21]. There is an evolving and promising role for 'less invasive' invasive functional assessments such as the quantitative flow ratio (QFR) that enables computation of FFR from a three-dimensional quantitative coronary angiography obtained from a diagnostic coronary angiogram without the need of advancing a pressure wire – this would clearly have a desired role in avoiding potential pressure wire complications.

The ISCHEMIA trial most certainly reinforces the importance of a tailored management to individual patients and encourages us to explore a more conservative approach if possible when considering the management of CCS especially in patients in whom the risk of an invasive strategy may outweigh any potential symptomatic benefit. Finally, the most important aspect of this topic are the patients and the quality of care they receive as a result of a chosen strategy and including them in decision making has always been essential and a cornerstone in tailoring and formulating a management plan regarding an invasive versus conservative strategy. Therefore, a key part of any management plan is to empower patients to reach a well-informed decision and subsequent consent regarding revascularisation in proven CCS in terms of their expectations around prognosis, anginal symptom control, preventing po-

tential future spontaneous MIs or indeed the risk of an invasive strategy, whether that is PCI or CABG. All these aspects need to be fully explained in light of the evidence so far.

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