**Atheroma or ischaemia: which is more important for managing patients with stable chest pain?**

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**Abstract**

In the evaluation and management of patients with stable chest pain/chronic coronary syndrome (CCS) cardiologists need to be able to weigh up the relative merits of managing these patients using either optimal therapy (OMT) alone or OMT plus revascularisation. These decisions rely on an understanding of both the presence and degree of coronary atheroma and myocardial ischaemia, and the impact that these have on patients’ symptoms and their prognosis. In this review we examine the relative impact of the anatomical and physiological assessment of patients with CCS, and how these can be used to achieve optimal and tailored therapy.

**Lay abstract**

There are a large number of patients with stable chest pain in the community who are not having a heart attack. This review looks at the relative merits of different investigation strategies that either assess whether a patient has coronary artery disease or whether they have a blood supply problem related to coronary disease.

**Tweetable abstract**

Finding the balance between coronary atheroma and myocardial ischaemia when investigating patients with chest pain; getting it right matters to our patients and also to the financial security of healthcare systems.

**Keywords**

Atheroma, ischaemia, chest pain, PCI, CABG, Prognosis, medical treatment,

**Executive summary**

**Introduction**

* Stable chest pain (chronic coronary syndrome) is a common presentation and the optimal management can be challenging given the conflicting data regarding the importance of coronary atheroma and myocardial ischaemia, as well as the potential relative benefits of OMT alone versus OMT plus revascularisation.

**Assessment of Coronary Atheroma: the anatomical approach**

* Identification of significant atheroma in the coronary tree in such patients indicates that optimal disease-modifying medication will offer prognostic benefit

**Myocardial Ischaemia: when, and in what way, is it important to the patient?**

* The presence of myocardial ischaemia, if extensive, also provides an indication of prognosis, which may be dose-dependent. Identification of vessel-specific, ideally lesion-specific, ischaemia allows for optimal targeting of revascularisation, and is also an effective way of relieving symptoms above and beyond anti-anginal therapy.

**Future perspective**

* Future strategies for patients with chronic coronary syndromes may focus on non-invasive identification of significant atheroma, which will trigger initiation of optimal disease-modifying and anti-anginal therapy. Should the patient have: (a) left main disease or (b) ongoing angina despite OMT, then revascularisation could be considered. The revascularisation strategy will be informed by assessment of vessel- and lesion-specific ischaemia.

**Summary Points**

* Stable chest pain (chronic coronary syndrome) is a common presentation and the optimal management can be challenging given the conflicting data regarding the importance of coronary atheroma and myocardial ischaemia, as well as the potential relative benefits of OMT alone versus OMT plus revascularisation.
* Identification of significant atheroma in the coronary tree in such patients indicates that optimal disease-modifying medication will offer prognostic benefit
* The presence of myocardial ischaemia, if extensive, also provides an indication of prognosis, which may be dose-dependent. Identification of vessel-specific, ideally lesion-specific, ischaemia allows for optimal targeting of revascularisation, and is also an effective way of relieving symptoms above and beyond anti-anginal therapy.
* Future strategies for patients with chronic coronary syndromes may focus on non-invasive identification of significant atheroma, which will trigger initiation of optimal disease-modifying and anti-anginal therapy. Should the patient have: (a) left main disease or (b) ongoing angina despite OMT, then revascularisation could be considered. The revascularisation strategy will be informed by assessment of vessel- and lesion-specific ischaemia.

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**Introduction**

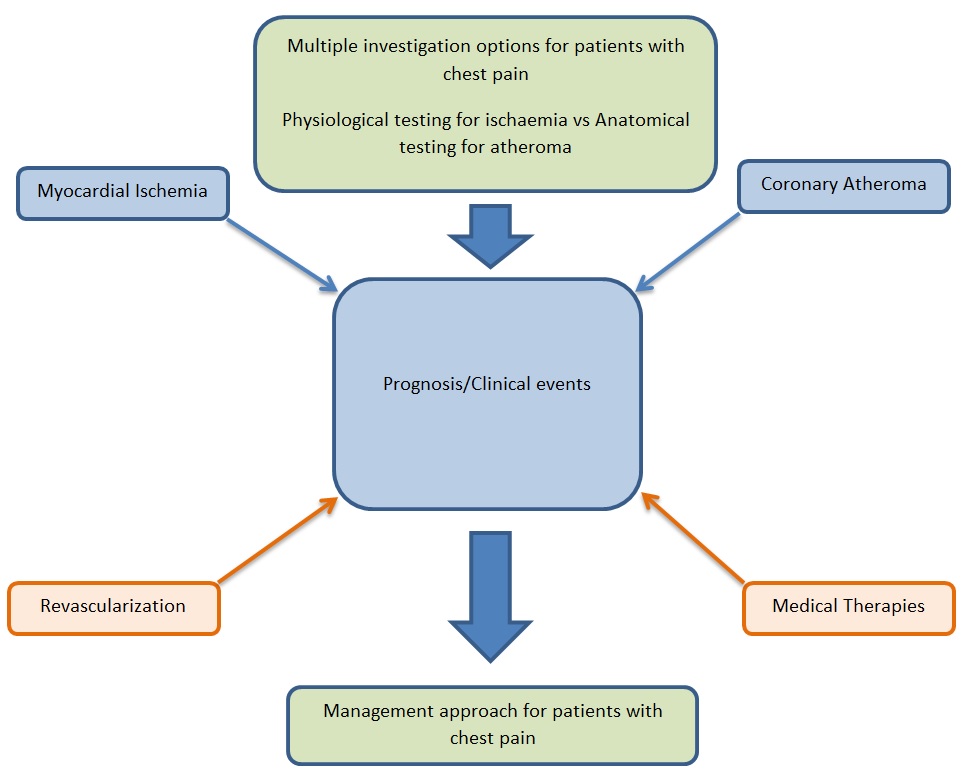
Coronary artery disease (CAD) remains a leading cause of global mortality [1,2]. Although there has been a decline in the number of deaths attributed to CAD in the UK, it is still responsible for mortality and morbidity that affects millions of people every year [3].

Chest pain is a common symptom, accounting for 1-2% of all consultations in primary care, [4] and increases the risk of being diagnosed with CAD in the following year by more than 18% [5]. More than 14% of all chest pain attendances to primary health care have been subsequently been attributed to CAD [6]. Similarly, chest pain is among the commonest presentations to the Emergency Department, being responsible for 6-11% of all adult attendances [7,8].

The initial assessment and management of patients presenting with chest pain which is felt clinically to be the result of stable angina, now labelled as a chronic coronary syndrome (CCS) is challenging, partly because of the wide choice of investigations that are available. This choice results in considerable heterogeneity in both clinical practice and advice in international guidelines. For example, the National Institute for Health and Clinical Excellence (NICE) CG95 Guidance for Chest Pain of recent Onset in the UK recommended computerized tomography coronary angiography (CTCA) as the first line diagnostic test based for patients presenting with symptoms suggestive of CAD with no prior history of CAD [9]. On the other hand, the European Society of Cardiology (ESC) recommends an assessment of the pre-test probability and likelihood of CAD based on patient characteristics, symptoms and risk factors to determine the imaging test of choice [10]. Similarly, the American College of Cardiology (ACC)/American Heart Association (AHA) use a pre-test probability model to guide further investigation [11,12].

The choice of initial investigations available for a population presenting with potential stable angina/CCS can be broadly categorised into 2 groups. (a) Anatomical imaging to assess the presence and extent of coronary atheroma, including invasive coronary angiography (ICA) and CTCA and (b) Functional imaging to assess the presence and extent of myocardial ischaemia, including stress echocardiography, stress nuclear myocardial perfusion scan, and stress cardiac magnetic resonance. A novel third group of tests is becoming available that can potentially assess for both atheroma and ischaemia burden, including fractional flow reserve-computed tomography (FFRCT) [13] and invasive angiogram-derived fractional flow reserve physiology[14].

Each of these investigations has its advantages, as well as its limitations. There is an array of factors that are taken into account by a clinician when choosing an approach to the investigation of such a patient, which include: ease of access, cost, current evidence base and guidelines, patient preference. Broadly speaking, the evidence base is shifting for patients with CCS. The identification of significant coronary atheroma and its implication for the initiation of disease-modifying medical therapy unequivocally produces a reduction in long term risk for these patients. The clinical applicability of demonstrable myocardial ischaemia in the individual also has potential prognostic implications, but its exact role in this process may be secondary to the anatomical considerations described above. Specifically, how the acquired knowledge regarding the locality and extent of ischaemia is translated into a bespoke management plan remains contentious[15–18]. The relative merits of the atheroma versus ischaemia approaches to investigation and management of a patient with stable angina (from now on, this term will be used interchangeably with CCS) are the focus for this review as illustrated [Figure 1].



**Figure 1: Examining the effect of coronary atheroma versus myocardial ischaemia, and disease modifying interventions to create a potential approach in managing patients with chest pain.**

**Assessment of Coronary Atheroma: the anatomical approach**

CAD is characterised by a chronic inflammatory process involving the vessel wall that leads to a progressive build up of atheroma [10]. This process can often start at an early age, as demonstrated by the high prevalence of coronary atherosclerosis seen in young adults [19]. This pathophysiological process may remain subclinical for many years until (a) it accumulates to a point that causes significant lumen stenosis, resulting in symptoms of angina, or (b) when an acute vascular inflammatory event leads to plaque rupture or erosion that initiates thrombus formation and acute coronary syndrome (ACS).

A strategy that investigates a patient presenting with stable angina by imaging for coronary atheroma can potentially address two important questions. Firstly, would the patient obtain prognostic benefit from disease-modifying therapy? Secondly, could the chest pain be due to the atheroma that is detected? Angiography, whether invasive or non-invasive, and to some extent coronary artery calcium scoring, can reliably answer the first question. However, on many occasions, such anatomical tests cannot, in their own right, answer the second.

Coronary artery calcification (CAC) is an established surrogate for the presence and extent of coronary atherosclerosis [20]. A wealth of data demonstrates a clear association between the amount of coronary artery calcification and the subsequent risk of both acute cardiac events and overall mortality[21–23]. For example, during 8 years follow up of symptomatic patients, Rijlaarsdam-Hermsen *et al.* found on univariable analysis that patients with a calcium score >100 Agatston units had a hazard ratio (HR) of 2.6 (95% confidence interval (CI) 1.2 – 5.5) compared to patients with a calcium score <100) and this HR increased to 4.6 (95%CI 2.1 – 9.5) in those with a score of 400 or more [24].. Similarly, there is a positive association between risk of major adverse cardiovascular events (MACE) and coronary calcium score in the PROMISE trial (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) with a calcium score of >400 associated with HR of 3.56 (95% CI 1.99 -6.36) at a median follow up of 26.1 months [25]. A recent meta-analysis also described a robust and independent association between increasing calcium score and risk of MACE in symptomatic patients (RR 5.71 (95%CI 3.98 – 8.19) with score >0 vs 0, RR 9.57 (95%CI 6.87 – 13.33) with score >100 vs 0, RR 5.08 (95%CI 3.52 – 7.34) with score >400 vs <100)[26]. Thus, detection of the overall atheroma burden using CAC scoring as a surrogate could be useful in determining to whom we should apply OMT. However, CAC testing would miss non-calcified coronary atheroma and will obviously not provide a functional assessment of the significance of the coronary disease in terms of whether it is responsible for inducible myocardial ischaemia, and is therefore a potential explanation for symptoms.

Coronary disease seen at angiography may or may not cause flow limitation and, despite this, in clinical practice, it is often classed as either “obstructive” or “non-obstructive” according to its visual appearance. It is clear that this pathway is flawed in a substantial proportion of these patients. Specifically, the label “obstructive”, if used to imply that the lesion is limiting flow to the extent that it results in reversible myocardial ischaemia, is inaccurate in around 30% of lesions, as determined in studies using the intracoronary pressure wire [27–29]. This discrepancy between the angiographic assessment of lesion severity, and its actual physiological consequence, can then lead to inaccurate, and potentially inappropriate, management [30]. The true value of the anatomical test is in establishing whether there is atheroma present, given the well-established link with clinical events, but especially because of the robust evidence demonstrating that disease-modifying medical therapy can alter the future risk.

The case that identification of coronary atheroma highlights patients at increased risk of clinical events is indeed strong. For example, Maddox *et al.* compared the one year outcome of more than 37,000 patients who had elective coronary angiography for anginal symptoms [31] and, on multivariable analysis, the hazard of MI at one year steadily increased with increasing numbers of vessels with non-obstructive CAD (which the study classed as a stenosis of ≥20% but ≤70%) compared with those with no apparent CAD (<20% stenosis) (one vessel HR 2.0 (95% CI 0.8 – 5.1), two vessel HR 4.6 (95%CI 2.0 – 10.5), three vessel or left main HR 19.5 (95%CI 9.9 -38.2))[31]. Furthermore, whilst 1 and 2 vessel non-obstructive CAD was not associated with one year mortality on multivariable analysis, 3 vessel CAD was, with a HR of 1.6 (95%CI 1.1 -2.5)[31]. These findings suggest a dose-dependent risk based on the total burden of coronary atherosclerosis. Likewise, Bittencourt *et al*. followed up 3242 patients for a median of 3.6 years following CT coronary angiography and found that patients with extensive non-obstructive CAD (<50% stenosis) affecting four or more coronary segments out of an 18 segment model) had a significantly higher rate of cardiovascular death or MI when compared to those with no CAD (HR 3.1 95%CI 1.3 – 6.9)[32]. In addition, even in patients with obstructive disease (≥50% stenosis), the additional burden of non-obstructive atheroma was shown to be associated with increasing event rates[32]. In fact, a validation study of the Computed Tomography-Leaman Score (CT-LeSc: a score for assessment of atherosclerotic burden based on the plaques characteristics, location and stenosis severity) found comparable survival (free of MI and cardiac death) among those with non-obstructive CAD (< 50% stenosis) with high atheroma burden (CT-LeSc >5) and those having obstructive disease (plaque causing ≥ 50% stenosis) and a similar total atheroma burden (78.6% vs 76.5% survival respectively, P=0.627)[33]. In addition, in the absence of ischaemia on single photon emission computed tomography (SPECT), high risk atheroma features (focal calcification in the plaque, location in the LMS or proximal LAD, disease in ≥ 4 segments) have been found to carry 23 times higher risk of cardiac events (a composite of cardiac death, MI, unstable angina (UA), and revascularisation) with similar event free survival to that of patient with ischaemia on SPECT[34].

Furthermore, a meta-analysis by Wang *et al* including 54 studies with 1,395,190 patients followed up for a median of 27 months described an 85% higher risk of cardiac events (death or MI) in patients with mild disease on invasive coronary angiogram or CTCA when compared to those with no CAD [35]. Specifically, there was much higher risk of MI in patients with non-obstructive CAD (≤50% stenosis) compared with those with no CAD (RR 3.37 (95% CI 2.16 – 5.28))[35]. This is consistent with the observation from both pathological and imaging studies that the majority of acute coronary syndromes arise at a site of non-severe coronary atheroma (< 50% stenosis) [36,37].

Having established the link between the presence and extent of coronary atheroma and the rate of clinical events, the next obvious question relates to whether the trajectory of this risk can be modified by medical intervention. Again, the literature provides unequivocal evidence that this is, indeed, the case. The most clear cut and high profile example of this is perhaps the 5 year outcome from the SCOT-HEART (CT coronary angiography in patients with suspected angina due to coronary heart disease) trial [38]. This trial randomised 4,146 patients referred to chest pain clinics to either standard care alone or standard care and CTCA. At 5 years, despite similar rates of invasive coronary angiography and revascularisation, there was a lower rate of non-fatal MI in the CTCA group (HR 0.60; 95% CI 0.41 to 0.87) which was the main driver behind the reduction in the combined primary endpoint (a combination of death related to coronary heart disease or non-fatal MI) (HR 0.59; 95% CI 0.41 to 0.84). This observation is most likely to be explained by the application of disease-modifying medical therapy in the group randomised to CTCA when they were found to have coronary atheroma. Specifically, the use of these therapies was around 3 times higher in those with CTCA-identified CAD compared with those without CTCA, despite similar 10 year cardiovascular risk scores [39]. Importantly, it is an effect that did not require any information regarding the possible presence or extent of myocardial ischaemia.

The prescription of disease-modifying prevention therapies for CAD has become common practice [40] that lower the risk of hospital re-admissions (HR 0.89; 95% CI 0.84–0.95; P<0.001) [41]. Statin therapy is particularly effective at outcome modification among patients with unobstructive CAD. For example, data from the CONFIRM registry (COroNary CT Angiography Evaluation For Clinical Outcomes: An InteRnational Multicenter Registry) demonstrated that statin therapy did reduce the risk of all-cause mortality in patients with unobstructive disease [42]. In this analysis, patients with unobstructive disease (1%-49% stenosis on CTCA) who had a Segment Involvement Score (SIS) (a score to assess atheroma burden by calculating the number of diseased coronary segments) of 2 or more had a higher risk of all-cause mortality while not on statin therapy in comparison to those with no CAD (HR 2.95; p=0.002). Interestingly, no such difference was seen in those with similar SIS but who were on statin therapy (HR 0.84; p=0.8). Similarly, mortality was significantly lower in patients with unobstructive CAD (1%–49% stenosis) who were on a statin (1.0% mortality) compared to those with similar disease but not taking statin therapy (2.2% mortality) in another study from the CONIFRM registry (P=0.001)[43]. This effect is predictable given that statin users have considerably slower progression of low attenuation and non-calcified atheroma [44,45]. Furthermore, aspirin was associated with a significant reduction in all-cause mortality (HR 0.649; 95% CI 0.492–0.857) among patients with unobstructive CAD (1%–49% stenosis), although this outcome was limited to patients in traditionally higher risk subgroups (age >65, hypertension, diabetes, dyslipidaemia, calcium score >100, and CKD) [46]. Finally, there is a wealth of evidence that angiotensin converting enzyme inhibitors (ACE-I) significantly reduce the medium term risk of clinical events such as heart attack, stroke and cardiac arrest from clinical studies, including HOPE (Heart Outcomes Prevention Evaluation) and EUROPA (European Trial on Reduction of cardiac events with Perindopril in patients with stable coronary artery disease) [47–49]. The beneficial effect of ACE-I in relation to patients with unobstructive CAD (<50% stenosis) was illustrated by a lower 6-month mortality (HR 0.31; 95% CI 0.03-0.78; p <0.004) in the EMMACE-2 (Evaluation of the Methods and Management of Acute Coronary Events) registry data [50].

Thus, the case that disease-modifying drug therapy improves the trajectory of risk for patients with even mild atheroma is robust and well established.

**Myocardial Ischaemia: when, and in what way, is it important to the patient?**

It is a common and important clinical challenge to determine whether the symptoms that a patient describes are due to myocardial ischaemia, particularly if it has already been established that coronary atheroma is present. This is because of the well established discrepancy between angiographic and haemodynamic “severity” of individual coronary lesions, which was described above. As documented earlier, clinicians can offer patients with established CAD an improved prognosis with disease-modifying therapy in the form of aspirin, statin and ACE inhibitor. However, above and beyond establishing if the patient has CAD, there may be important additional benefits from also determining whether they have ischaemia, how extensive it is and the precise locality. For example, if the symptoms are not completely typical of angina (shortness of breath or atypical chest pain in particular) then it is important to make sure that there is ischaemia as well as just noting the presence of CAD. Atheroma is common and so its presence does not necessarily explain such symptoms. Further, if the patient requires revascularisation, by virtue of ongoing symptoms, then the target for such intervention may require localisation of patient-specific and ideally vessel/lesion-specific ischaemia. The exact management consequence of determining the presence and extent of myocardial ischaemia, however, is contentious.

As a foundation to addressing this question, the prognostic association between myocardial ischaemia and clinical outcome, including mortality in some instances, has been well described. For example, in a large multicentre registry of more than 7,000 patients who were referred for positron emission tomography myocardial perfusion imaging (PET MPI) for clinical reasons (angina in 66% of the cases), the mortality at a median of 2.2 years follow up was highest in the patients with the severely abnormal stress PET (HR 4.9 (95%CI 2.5 – 9.6) compared with those with a normal stress [51]. In addition, the addition of these data to clinical information provided a significant improvement in the C-statistic for discrimination of cardiac death (0.805 (95%CI 0.772 – 0.838) increasing to 0.839 (95%CI 0.809 – 0.869)[52]. Furthermore, risk adjusted event free survival curves in this study showed clear separation in the group who had 0% ischaemia and incrementally worsening for patients with 10%, 20% and 30% ischemic myocardium. Similarly, the presence and extent of myocardial ischaemia on stress cardiac magnetic resonance has been shown to be an independent predictor of cardiac death and non-fatal MI in several studies [53–56].

Having established that the presence and extent of myocardial ischaemia is indeed associated with clinical outcome, the question again naturally arises: can treatment of ischaemia by revascularisation affect prognosis in patients with stable angina/CCS? This goes above and beyond the well established observation that revascularisation in patients who are experiencing myocardial ischaemia as a consequence of coronary disease is an effective treatment for those symptoms[57,58]. Hachamovitch *et al.* presented an observational study of more than 10,000 patients in which they described a short term (mean follow of 1.9 years) reduction in cardiac mortality (2.0% vs 6.7%; p<0.02) with revascularisation compared to medical therapy alone in patients with high burden (>20%) of myocardial ischaemia detected on stress myocardial perfusion scan (MPS)[59]. Interestingly, the survival curves started to separate at 10-12.5% burden of ischaemia in favour for revascularisation [59]. A decade later, a study in Japan followed up more than 4500 patients with variable degrees of ischaemia on MPS and found that revascularisation could reduce cardiac events, including cardiac death, in patients with more than mild burden of ischaemia [60]. Multiple other studies have also suggested that there is a prognostic benefit derived from revascularisation in patients with significant myocardial ischaemia [61–63]. Naturally, however, these data are associated with the inherent limitations seen in observational studies.

Further evidence that detectable ischaemia is associated with clinical events is demonstrated by the outcomes of patients whom had an assessment of the vessel Fractional Flow Reserve (FFR) and were subsequently treated medically [64]. In this study, which included 607 patients, the measured FFR was associated with the 2 year rate of major adverse cardiac events (MACE, defined as the composite of cardiovascular (CV) death, target vessel– related MI, and ischaemia-driven target vessel revascularisation (TVR) (both urgent and non-urgent). The conclusion was that “In patients with stable coronary disease, stenosis severity as assessed by FFR is a major and independent predictor of lesion-related outcome”[64].

The potential clinical value of patient- and vessel-specific ischaemia in improving clinical outcomes has been vividly demonstrated in the series of randomised trials (including DEFER (Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis), FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and FAME 2 (Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease)) that utilised FFR guidance, as compared to angiographic guidance alone, in patients committed to percutaneous coronary intervention (PCI) as their front line therapy. The DEFER Study randomized 325 patients who were listed for PCI (with no prior evidence of ischaemia), in whom the FFR was greater than 0.75, into either performing or deferring PCI. After 5 years there was similar survival free of cardiac events (All cause death, MI, CABG, PCI) in the defer and perform PCI groups (80% vs 73%; p = 0.52), hence demonstrating the safety of deferring PCI in patients with non-ischemic lesions on FFR [65]. In fact, even at 15 year follow up, the mortality was similar in the defer and perform PCI groups (RR 1.06; 95% CI: 0.69-1.62). Interestingly, there was a reduction in the hazard of MI in the defer PCI group (RR 0.22; 95% CI: 0.05-0.99) [66]. Further supporting evidence for the concept that ischaemia should be the targeted substrate for revascularisation are the FAME studies. The original FAME study randomised more than 1000 patients with multivessel coronary disease to either angiographically-guided management or pressure wire-directed management of the disease. This study showed significantly lower composite outcome of death, MI, and repeat revascularisation after one year of follow up in favour of those managed using pressure wire (13.2% vs 18.3%; P=0.02)[67]. This was achieved despite fewer stented vessels, with less stents in the pressure-wire directed group.

FAME 2 randomised 888 patients with pressure wire proven ischemic lesions (≤0.80) to medical therapy or medical therapy combined with PCI. There was a marked reduction in the composite primary endpoint of mortality, MI, or urgent revascularisation in favour of PCI (4.3% vs 12.7%; HR 0.32; 95%CI 0.19 to 0.53) which was extensively driven by the urgent revascularisation component [28]. Subsequently, similar clinical outcome data has been demonstrated in studies using the instantaneous wave-free ratio (iFR) measurement as an invasive assessment of ischaemia [68,69].

In summary, the pressure wire studies show: (a) that the outcome from stenting lesions that are non-ischaemic is worse than OMT alone; (b) that FFR guidance in multivessel disease is associated with a better clinical outcome than angiographic guidance, despite less stents and less vessels stented; (c) that OMT alone for patients with lesions that are ischaemic is associated with higher event rate than OMT plus PCI targeted to those lesions.

Thus, an evidence base exists to suggest that ischaemia does indeed play a role in clinical outcome, and that, certainly for patients being considered for PCI, targeted application of stenting to ischaemic patients and lesions is associated with a better clinical outcome. However, the persuasive nature of all the pressure wire data needs to be considered in the context of two large randomised trials that have compared clinical outcome of OMT alone versus OMT plus revascularisation in stable patients. When comparing the results of these trials with the pressure wire studies, it is important to note that the outcome advantage in the pressure wire studies was driven by events other than mortality. Specifically, the pressure wire studies were all powered using a composite primary endpoint. In fact, *no mortality advantage* was seen in these data: rather, the driver to the benefit of pressure wire is either via a reduction in revascularisation or MI. Taking note of this single point helps to allow for an apparent discrepancy between trial results that has undeservedly caused much confusion amongst clinical staff seeking to do the best for their patients. Specifically, interpretation of the outcome of trials looking for a “prognostic” difference between OMT alone and OMT plus revascularisation (dominated by PCI) can now be undertaken, armed with this observation about the pressure wire trials.

However, before moving on to analyse these trials in detail, which will be critical to answering the question posed by this review, it is natural to consider whether there are any data that do demonstrate a mortality advantage to the use of pressure wire (i.e. ischaemia) guidance. The observational study by Volz *et al.* provides an interesting perspective on this question [70]. The study is a simple description of the mortality of 23,860 patients undergoing PCI for stable angina, of whom 3,367 had pressure wire guidance. The pressure wire group had lower adjusted risk estimates for all-cause mortality (HR 0.81; 95% CI: 0.73 to 0.89), and stent thrombosis and restenosis (HR: 0.74; 95% CI: 0.57 to 0.96) after a median follow-up of 4.7 years (range 0 to 11.2 years). Perhaps the most interesting thing about the results is that the separation in mortality started at about 1 year and then continued to get wider out to an extended follow up of 11 years in a few patients. This raises the suspicion that ischaemia-driven management of patients is effective in improving longer term survival, whilst the difference may not be apparent for some years after the index decision.

The need for formal, randomised comparison of OMT alone versus revascularisation with OMT in patients with stable angina/CCS is obvious and clear cut. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial was the first trial to examine the effect of OMT plus revascularisation with PCI compared to OMT alone [71]. With more than 2000 subjects included and over 400 primary events (death from any cause and non-fatal MI) with a median of 4.6 years of follow up, no significant prognostic advantage was observed in the revascularisation group. As expected, PCI was found to be superior in reducing ischaemia compared to medical therapy alone in the COURAGE trial nuclear substudy but this did not translate to a risk adjusted prognostic effect [72]. However, an analysis of COURAGE highlights some of the limitations that are inherent in randomised clinical trials when attempting to answer such questions Specifically, a number of issues should be considered when interpreting this trial from a real world clinical perspective [73]. Firstly, only 6% of over 35,000 patients screened for participation in the study were eventually randomised. The relevance of these findings in our everyday decision-making must be questioned. Secondly, the relief of angina symptoms was much greater in the PCI group: not a bad outcome given that this is what the patients would have been seeking when they first presented. In fact, at follow up, 32.6% of the OMT group had undergone revascularisation, mainly because their symptoms were not well controlled by their medication. COURAGE thus actually provided us with this important information: that there is no prognostic advantage of OMT plus PCI versus OMT alone in these patients with stable angina, but that PCI was much more effective at treating angina. This is an eerily similar message to the (equally contentious) ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, which was presented recently.

In 2020, The ISCHEMIA trialists reported their findings regarding the effect of a strategy of OMT plus coronary angiography and revascularisation, where appropriate, versus OMT alone, in patients with stable angina with moderate to severe myocardial ischaemia [74]. At 3.2 years follow up, there was no significant difference between the two groups in the primary endpoint, which was a composite of cardiovascular death, MI, hospitalisation for unstable angina, heart failure or cardiac arrest. Once again, this led to a headline result: that revascularisation had nothing to offer patients with stable angina above and beyond OMT. However, as is always the case, such an important trial deserves and demands a much greater degree of scrutiny to identify all the important findings it contains. To begin with, 12% of the population had only mild, or no, ischaemia. Further and surprisingly, just over a third of the study population had no angina when they were randomised. Despite this, by the time of the primary endpoint, 28% of the OMT alone group had undergone coronary angiography and 23% of them had had revascularisation because of ongoing symptoms. This is despite the study protocol excluding class III and IV angina, and patients with left main stenosis at screening. Not surprisingly, there was a highly statistically significant improvement in angina status in the revascularisation group compared to OMT alone. In addition, a subsequent publication detailed a significantly higher rate of MI in the OMT alone group, together with the observation that having MI was associated with higher mortality [75].

ISCHEMIA tells us that revascularisation does not reduce mortality above and beyond OMT, a message entirely consistent with COURAGE, and, when examined carefully with the FFR trials (DEFER, FAME and FAME2). It also tells us that if angina persists on OMT, revascularisation is an excellent treatment to settle this symptom. A significant reduction in spontaneous MI in the OMT plus invasive group is of potential interest: it is possible that as the follow up period extends a difference in clinical outcome may become apparent, judging by the data described above from the SCAAR Registry… although this is simple speculation. However, in term of mortality it would be unlikely to expect a trial demonstrating a benefit from revascularization of ischaemic lesions given the exclusion of high risk patients due to understandable ethical reasons.

**Ischaemia or atheroma: why is there a discrepancy?**

Based upon ISCHEMIA, and COURAGE before it, the clinical evidence is strong that routine revascularisation does not reduce mortality above and beyond OMT in patients with stable angina. Given the evidence from both randomised trials and observational studies of the prognostic association between (a) the presence and extent of ischaemia and subsequent clinical events and (b) pressure wire-directed PCI and clinical outcomes, why does this not translate into a stepwise improvement in outcome/mortality when revascularisation is added to OMT in CCS? There are several possible answers to this question.

First, identification of significant atheroma in the coronary circulation is consistently associated, in a dose dependent manner, with subsequent MI and death. For example, anatomical burden (atheroma causing more than 50% stenosis in a coronary segment) was a reliable predictor of future MIs and deaths in the COURAGE trial in a much more clear cut fashion than was the case with ischaemic burden [76]. These results are consistent with those of a sub-analysis of the PROMISE trial, which demonstrated the discriminatory role of describing the extent of coronary atheroma by CTCA in patients presenting with suspected angina, even in the absence of any functional testing for ischaemia, for predicting the primary endpoint of death, myocardial infarction and hospitalisation for unstable angina [77].

Second, the consistent power of disease-modifying OMT to improve prognosis, exemplified best by the previously discussed SCOT-HEART 5 year results, may well dilute an additional prognostic effect of revascularisation in some patients.

Third, the comparison in both COURAGE and ISCHEMIA never really was between OMT alone and OMT plus revascularisation because in both cases around a third of the patients in the OMT group underwent coronary angiography and, where appropriate, revascularisation, on the basis of ongoing angina. What would have been the outcome of a comparison between these two groups if such cross over to the invasive strategy had not been permitted? Clearly, such a practice would have been unethical and inappropriate, but, as a thought experiment it is justified in provoking speculation that we have never actually seen a true comparison with “OMT alone” as a strategy.

Fourth, by excluding high risk groups such as those with class III/IV angina, those in whom angina had already broken through medical treatment, those with left main lesions and those with reduced left ventricular function, the ISCHEMIA trial has eliminated a population of patients in whom we *would* expect there to be a high chance of prognostic benefit from revascularisation. Once again, the thought experiment that runs ISCHEMA again, but this time with all of those groups included, does invite speculation about a rather different outcome?

Fifth, the truth about the wealth of data (for example from DEFER, FAME and FAME2) presented above suggesting prognostic advantage for an ischaemia-directed approach is that the favourable clinical outcomes very rarely included a mortality difference. Rather, the “prognostic” association with ischaemia burden, and the clinical outcome advantages of pressure wire-directed therapy in PCI were based upon composite endpoints and the driver for the outcomes that they described were components (such as revascularisation or MI) other than mortality itself. In this context, there is therefore no real discrepancy between those observations and COURAGE or ISCHEMIA. In particular, the reduction in spontaneous MI seen in the invasive group in ISCHEMIA, is consistent with much of the pressure wire data, and could yet translate into a true prognostic advantage.

**Future perspective**

The appropriateness of establishing the presence and extent of coronary atheroma in patients with stable angina/chronic coronary syndrome, without left main disease, and then committing them to OMT, consisting of both disease-modifying and anti-anginal therapy, is now well established and unequivocal, based upon a symptomatic and prognostic advantage. Therefore, the most appropriate initial test would be in the form of CTCA to identify patients with coronary atheroma who would benefit from medical therapy but also avoid unnecessary treatment for patients with no coronary disease whatsoever by not applying a blanket atheroma treatment to all patient with chest pain. This is also in contrast to initial traditional ischaemia tests that would miss a non-obstructing but important prognostic coronary atheroma. The role for assessment of ischaemia in such patients may become reserved for those patients who continue to have angina on OMT. Such patients may then be considered for tests for ischaemia: in many cases the obvious choice in this regard will be FFRCT, given that perhaps the majority will have had a CTCA as their front line test with which to establish the diagnosis. This approach has the advantage that it will provide diagnostic certainty, particularly in those with atypical symptoms, and also allow some planning for the anticipated revascularisation which will become inevitable under these circumstances for patients whose angina doesn’t settle on tablets. Patients would then undergo invasive angiography if they need PCI. In Addition, the added benefit of this approach would save the cost of FFRct to the health system until the time it is actually required when the patient continue to have angina despite OMT which may occur other few weeks, months, or possibly never. Furthermore, it is increasingly likely, as CTCA/FFRCT technology improves, that many patients with severe coronary disease may be accepted for CABG without the need for invasive angiography at all [Figure 2].

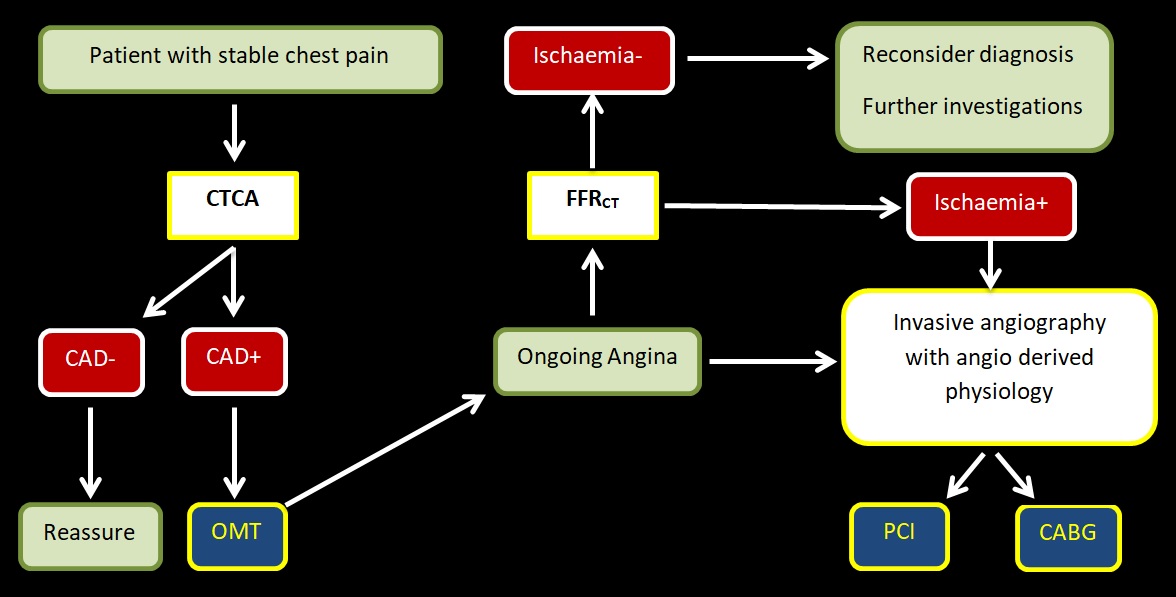


Figure 2: The potential future pathway for the investigation and management of patients presenting with stable chest pain

The role for routine and comprehensive use of CTCA and FFRCT in this population has not been tested when compared to frontline CTCA alone. However, the FORECAST trial (Fractional Flow Reserve Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain) showed no clinical outcome advantage in a randomised comparison between CTCA with selective FFRCT and routine assessment, which included CTCA in over 60% of the patients, in patients with stable angina[78]. However, there was a 22% reduction in the number of patients in the CTCA/ FFRCT group that needed invasive angiography.

There are potential areas for further improvement in the management of patients with CCS. Firstly, an ability to modify the risk of acute coronary events using more sophisticated targeting of the pathophysiological processes of atherogenesis and plaque erosion/rupture using anti-inflammatory agents has been hinted at by studies such as the CANTOS (Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease) [79] and LoDoCo2 (Colchicine in Patients with Chronic Coronary Disease) trials[80]. Even before this, the exciting prospect of biomarkers that are much better than current clinical factors in identifying candidates for primary prevention pharmacology, including especially high sensitivity troponins, is already taking shape, based upon data from various patient populations[81,82]. Alternatively, there is the promise of individualised systematic identification of high risk plaques within individuals using a variety of potential tools, and this could potentially be coupled with tailored pharmacological, and perhaps even intracoronary, interventions.

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