Revascularization in stable coronary artery disease

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Abstract

Management of stable coronary artery disease (CAD) centers on medication to prevent myocardial infarction and death. Many anti-anginal medications also have benefit for reducing symptoms, and have been proven to be effective against placebo control. Before effective preventive medications were available, patients with stable CAD often underwent revascularization with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), on the plausible assumption that these procedures would prevent adverse events and reduce symptoms. However, recent randomized controlled trials have cast doubt on these assumptions.

Considering results from the recent ISCHEMIA trial, we discuss the evidence base that underpins revascularization for stable CAD in contemporary practice. We also focus on patient groups at high risk of myocardial infarction and death, for whom revascularization is often recommended. We outline the areas of uncertainty, unanswered research questions, and key areas of potential miscommunication in doctor-patient consultations.

Introduction

Stable coronary artery disease (CAD) refers to the presence of atheromatous plaque within the epicardial coronary arteries.1 This diagnosis may, or may not, coexist with a clinical syndrome of stable angina, namely chest discomfort in response to physical or emotional stress.2

Angina can result from a supply-demand imbalance of blood flow through the myocardium versus the heart’s metabolic requirements during stress. This imbalance can be detected with dynamic electrocardiographic features or reversible perfusion defects during stress testing, leading to diagnosis of a third clinical entity: myocardial ischemia.3

Critically, only some patients with stable CAD have ischemia, and only some with ischemia have angina. Understanding these distinctions is key to an accurate understanding of the contemporary role of revascularization, as a treatment option in stable CAD.

In this review we present and discuss the evidence supporting revascularization in stable CAD. The review is aimed at clinicians assessing patients with chest pain and coronary artery disease in a stable outpatient setting. It aims to summarize a large and growing evidence base in the field, highlight areas of controversy, and discuss topics for future clinical trials.

Sources and selection criteria

We performed a structured search of PubMed from inception to 13 May 2021 to identify all randomized controlled trials (RCTs) of revascularization (percutaneous coronary intervention, PCI, or coronary artery bypass graft surgery, CABG) versus a conservative approach for the management of stable CAD. We included trials that compared one revascularization strategy with another (PCI vs CABG).

The search terms are available in the supplementary appendix.

We excluded any study design that was not an RCT, used alternative techniques of revascularization (such as transmyocardial laser revascularization), trials studying alternative patient populations, and trials that did not report clinical endpoints.

Two authors independently reviewed the search results. Additional trials were identified through a hand search of references (fig 1).

When is coronary artery disease not stable?

Management of stable CAD differs from that of acute complications of CAD, despite the two presentations having the same root cause, namely atherosclerosis.4 In ST elevation myocardial infarction (STEMI), thrombosis resulting from plaque rupture rapidly and completely occludes the arterial lumen, causing infarction of the subtended myocardium. Emergency procedural intervention to reopen the artery reduces mortality in this setting.5 Acute presentations can also occur owing to dramatically increased demand rather than reduced supply. This phenomenon, type II myocardial infarction, can occur without thrombosis.
in situations such as sepsis; for these events no evidence suggests that procedural interventions are beneficial.6

It seems logical to assume that if an acute coronary syndrome (ACS) event needs emergency procedural intervention at any time of day or night, the chronic version of the same underlying disease should need the same intervention, but less urgently. This would be true only if all patients with stable CAD progressed inexorably to ACS, and coronary intervention was equally effective in preventing events in stable CAD as it is in ACS.

Fortunately, with modern medication, progression from stable CAD to ACS is rare. Moreover, in a patient who typically has multiple regions of atherosclerosis throughout the coronary tree, the site of a plaque rupture and thrombosis is not predictable, and therefore inserting a stent at the narrowest point may do nothing to prevent future events.7 The European Society of Cardiology (ESC) recently suggested renaming stable CAD “chronic coronary syndrome.” The problem with this term is that it emphasizes the similarities, rather than the differences, between the acute and chronic presentations of CAD.8

**Treatments for stable CAD**

**Medical therapy**

*Risk reduction medical therapy*

When managing stable CAD, the priorities are preventing myocardial infarction and death, irrespective of the presence of myocardial ischemia or angina. Aspirin and statins are well established interventions for these endpoints.9 10 Angiotensin converting enzyme inhibitors and aldosterone receptor antagonists, lipid lowering with PCSK9 inhibitors, ezetimibe, icosapent ethyl, and the addition of antithrombotic therapy with low dose rivaroxaban, have also been shown to reduce composite endpoints of major adverse cardiovascular events.11-17 These agents, together with control of blood pressure and glucose, and smoking cessation, are sometimes described as “optimal medical therapy.”

*Symptom reduction medical therapy*

The next step in management is control of angina in patients who are symptomatic.

Medications shown to reduce angina include: β blockers, calcium antagonists, long and short acting nitrates, nicorandil, ranolazine, and ivabradine. These medications are recommended as the initial
strategy to control symptoms in stable CAD, with a stepwise approach to introduction and up-titration of agents. Angina can occur without obstruction of the major coronary arteries. It can arise from microcirculatory abnormalities that are not visible on a coronary angiogram. Exertional chest discomfort in the absence of visible CAD is referred to as “microvascular angina.” This is considered a separate disease from angina caused by visible coronary obstruction and can be treated with anti-anginal medications which do not open atherosclerotic vessels. Therefore, the major mechanism of benefit from these medications must be either through altering the microvasculature or through global effects such as reducing heart rate, blood pressure, or intracardiac pressures.

Percutaneous coronary intervention
In 1977 Andreas Grünzig performed the first PCI to treat anginal symptoms. After more than four decades of technical progress and evolution, contemporary PCI is performed with implantation of third generation drug eluting stents, preferably guided by invasive physiology and optimized with intravascular imaging.

Coronary artery bypass graft surgery
CABG surgery predates the advent of PCI and was the original technique designed to restore afferent arterial flow across a stenosis. It involves the anastomosis of harvested venous and arterial grafts to coronary arteries, distal to a stenosis, improving perfusion in the distal coronary bed and myocardium.

Revascularization for prevention of death and myocardial infarction
CABG v no CABG
Early trials of CABG predated not only PCI but also the medications we now know prevent myocardial infarction and death. The Veterans Affairs Study, enrolling from 1972 and 1974, showed no significant survival advantage at 11 years for patients who underwent CABG. Non-prespecified subgroup analysis did find subgroups in whom survival was better with CABG, namely patients with three vessel disease and left ventricular impairment.

Taken together with the Coronary Artery Surgery Study (CASS) and the European Coronary Surgery Study [as on page 13] (ECSS), meta-analysis showed favorable results for CABG versus no CABG. CABG has the best opportunity to reduce events when there are many myocardial infarctions and deaths to prevent in the follow-up period, to offset the upfront procedural risks. The best era in which to test CABG to show a benefit was therefore the 1970s and 1980s. While these trials differed slightly in the patient groups recruited, they all were conducted before the introduction of statins and the routine use of aspirin.

These outdated revascularization trials have, to this day, become the anchoring evidence for CABG in stable CAD. Trials of revascularization are summarized in table 1.

Revascularization in the era of PCI
The first PCI was balloon angioplasty with no stent, performed to relieve angina. CABG had been accepted as beneficial prognostically, and PCI was therefore tested for a similar prognostic benefit.

The first trial to assess PCI was the Medicine Angioplasty or Surgery Study (MASS) trial, randomizing to three methods: CABG, balloon angioplasty, and no revascularization. Balloon angioplasty (ie, with no stent) is associated with high rates of re-stenosis. This was reflected in the results, in which the angioplasty and no-revascularization arms had a significantly higher rate of refractory angina that required a revascularization procedure. Rates of myocardial infarction and death, however, were not significantly different between the arms.

The subsequent Randomized Intervention in the Treatment of Angina (RITA-2) trial of 1997, surprisingly, showed a significantly higher rate of the primary endpoints (myocardial infarction and death) in the angioplasty arm.

The second Medication, Angioplasty or Surgery Study (MASS-2), with 611 patients, was three times the size of its predecessor and introduced stents in the angioplasty arm. It was the first trial to require not only coronary stenosis but also “ischemia,” which could be detected on a test or inferred from symptoms. This again showed significantly higher rates of revascularization for angina with PCI, but no difference in death or myocardial infarction between arms.

These early trials were too small to detect reduction of cardiovascular events, and because of their era omitted most of what we now consider essential medical therapy.

Arrival of risk reduction medical therapy
A new chapter of revascularization trials began when it was recognized that the incremental effect of revascularization should be measured with both arms receiving aspirin and statins.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial randomized 2287 patients to PCI versus no PCI, with more than 90% in each arm receiving aspirin and more than 90% in each arm receiving statin alongside other guideline directed medical therapy. Unexpectedly, even over five years, no significant difference was seen in the primary endpoint between arms.

Disappointment in the trial results fueled a retrospective search for criticisms of its design. One frequent allegation was that COURAGE did not include ischemia as an entry criterion. However, all patients had non-invasive objective evidence of ischemia before inclusion, 88% of patients had angina at baseline, and those without angina had at least one angiographic stenosis ≥80%.

Focusing exclusively on patients with diabetes, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial divided patients into those suitable for PCI, and those suitable for CABG.
### Table 1 | A summary of trials comparing revascularization with medical therapy alone for prognosis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion criteria</th>
<th>Mode of revascularization</th>
<th>Risk reduction (medical therapy)</th>
<th>n</th>
<th>Definition of non-fatal myocardial infarction</th>
<th>Primary endpoint</th>
<th>Follow-up duration</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASS 1983</td>
<td>Single or multivessel CAD, not including LMS</td>
<td>50% CABG, 50% no CABG</td>
<td>None (β blockers and nitrates)</td>
<td>780</td>
<td>New significant Q waves on ECG</td>
<td>All-cause mortality</td>
<td>5 years</td>
<td>No difference in mortality between CABG and no CABG (7.4% vs 9.2%, P=0.34)</td>
</tr>
<tr>
<td>CASS Extended follow-up 1990</td>
<td>Single or multivessel CAD including LMS</td>
<td>50% CABG, 50% no CABG</td>
<td>None (β blockers and nitrates)</td>
<td>780</td>
<td>New significant Q waves on ECG</td>
<td>All-cause mortality, myocardial infarction</td>
<td>10 years</td>
<td>No difference in mortality and myocardial infarction between CABG and no CABG (survival free from death AND myocardial infarction 69% in no CABG group, 67% in CABG group, P=0.41)</td>
</tr>
<tr>
<td>ECSS 1983</td>
<td>Multivessel CAD including patients with LMS stenosis</td>
<td>51% CABG, 49% no CABG</td>
<td>None (β blockers and nitrates)</td>
<td>768</td>
<td>Not specified</td>
<td>Survival (%)</td>
<td>8 years</td>
<td>Improved survival with CABG compared with no CABG (survival 88.6% in CABG group and 79.9% in the no CABG group, P=0.0013)</td>
</tr>
<tr>
<td>ECSS Extended follow-up 1988</td>
<td>Multivessel CAD including patients with LMS stenosis</td>
<td>51% CABG, 49% no CABG</td>
<td>None (β blockers and nitrates)</td>
<td>768</td>
<td>Not specified</td>
<td>Survival (%)</td>
<td>12 years</td>
<td>Increased risk of death and myocardial infarction with balloon angioplasty (absolute difference 3.0% (95% CI 0.4% to 5.7%, P=0.02))</td>
</tr>
<tr>
<td>Veterans Affairs Extended follow-up 1992</td>
<td>Single or multivessel CAD including patients with LMS stenosis</td>
<td>48% CABG, 52% no CABG</td>
<td>None (β blockers and nitrates)</td>
<td>686</td>
<td>New Q waves or symptoms of myocardial infarction with cardiac enzyme elevation</td>
<td>All-cause mortality</td>
<td>18 years</td>
<td>No difference in survival between CABG and no CABG (30% with CABG, 33% with no CABG, P=0.60)</td>
</tr>
<tr>
<td>STICH 2011</td>
<td>LVEF &lt;35% CAD suitable for revascularization</td>
<td>50% CABG, 50% no CABG</td>
<td>Aspirin, statins, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers</td>
<td>1212</td>
<td>Increase in cardiac enzymes AND typical myocardial infarction presentation OR typical ECG changes</td>
<td>All-cause mortality</td>
<td>4.7 years</td>
<td>No difference in mortality between CABG and no CABG (HR 0.86, 95% CI 0.72 to 1.04, P=0.12)</td>
</tr>
<tr>
<td>MASS 1995</td>
<td>Proximal LAD only, &gt;80% stenosis</td>
<td>33% CABG, 34% balloon angioplasty</td>
<td>None</td>
<td>214</td>
<td>New Q waves in 2 leads OR symptoms of myocardial infarction with CK-MB &gt;3 × ULN</td>
<td>Cardiac death, myocardial infarction, refractory angina requiring revascularization</td>
<td>3.5 years</td>
<td>Reduced risk of primary endpoint with CABG compared with balloon angioplasty and no revascularization arms (3%, 24%, and 17%, respectively, CABG v balloon angioplasty, P=0.0002)</td>
</tr>
<tr>
<td>RITA-2 1997</td>
<td>≥1 vessel CAD</td>
<td>50% balloon angioplasty</td>
<td>Aspirin</td>
<td>1018</td>
<td>New Q waves OR symptoms of myocardial infarction with non-Q wave ECG changes and 2 cardiac enzymes raised &gt;2 × ULN</td>
<td>All-cause mortality and myocardial infarction</td>
<td>2.7 years</td>
<td>Increased risk of death and myocardial infarction with balloon angioplasty (absolute difference 3.0% (95% CI 0.4% to 5.7%, P=0.02))</td>
</tr>
<tr>
<td>RITA-2 2003 (7 year follow-up)</td>
<td>≥1 vessel CAD</td>
<td>50% balloon angioplasty</td>
<td>Aspirin</td>
<td>1018</td>
<td>New Q waves OR symptoms of myocardial infarction with non-Q wave ECG changes and 2 cardiac enzymes raised &gt;2 × ULN</td>
<td>All-cause mortality and myocardial infarction</td>
<td>7 years</td>
<td>No difference in rates of death and myocardial infarction (absolute difference 2.2%, 95% CI -2.0% to 6.4%, P=0.21)</td>
</tr>
<tr>
<td>AVERT 1999</td>
<td>≥1 vessel CAD with ≥50% stenosis</td>
<td>52% PCI, 48% no PCI</td>
<td>Atorvastatin, aspirin</td>
<td>341</td>
<td>TIMI definition</td>
<td>Cardiac death, resuscitation after cardiac arrest, non-fatal myocardial infarction, cerebrovascular accident, CABG, angioplasty, worsening angina with objective evidence resulting in hospitalization</td>
<td>1.5 years</td>
<td>Reduced risk of primary endpoint with atorvastatin compared with PCI (RRR 36%, P=0.045, non-significant when significance level adjusted to 0.045 for interim analysis)</td>
</tr>
<tr>
<td>MASS II 2003</td>
<td>≥2 vessel proximal CAD Ischemia</td>
<td>33% CABG, 34% PCI</td>
<td>Aspirin, statins</td>
<td>611</td>
<td>New Q waves in 2 leads OR symptoms of myocardial infarction with CK-MB &gt;3 × ULN</td>
<td>Cardiac death, myocardial infarction, or refractory angina requiring revascularization</td>
<td>1 year</td>
<td>Higher rate of primary endpoint in PCI group than no revascularization or CABG (24.3% of PCI group, 14.3% of no revascularization and 6.4% of CABG group, P=0.0001)</td>
</tr>
<tr>
<td>MASS II Extended follow-up 2010</td>
<td>≥2 vessel proximal CAD Ischemia</td>
<td>33% CABG, 34% PCI</td>
<td>Aspirin, statins</td>
<td>611</td>
<td>New Q waves in 2 leads OR symptoms of myocardial infarction with CK-MB &gt;3 × ULN</td>
<td>Cardiac death, myocardial infarction, or refractory angina requiring revascularization</td>
<td>10 years</td>
<td>No difference in myocardial infarction or death with CABG, PCI, or no revascularization (survival 96.0%, 95.6%, and 98.5%, respectively)</td>
</tr>
</tbody>
</table>

(Continued)
### Table 1 | Continued

<table>
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<tr>
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<th>Primary endpoint</th>
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</tr>
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<tbody>
<tr>
<td>COURAGE 2007</td>
<td>≥1 vessel CAD</td>
<td>50% PCI</td>
<td>Aspirin and/or clopidogrel, simvastatin, ezetimibe</td>
<td>2287</td>
<td>Presentation consistent with ACS and Q waves in ≥2 leads or positive cardiac bio-markers OR silent myocardial infarction, as detected by abnormal Q waves, was confirmed by a core laboratory</td>
<td>Death, myocardial infarction, and stroke</td>
<td>4.6 years</td>
<td>No difference in rate of primary endpoint with PCI when added to MT (HR 1.05, 95% CI 0.87 to 1.27, P=0.62)</td>
</tr>
<tr>
<td>COURAGE Extended follow-up 2015</td>
<td>≥1 vessel CAD</td>
<td>50% PCI</td>
<td>Aspirin and/or clopidogrel, simvastatin, ezetimibe</td>
<td>1211</td>
<td>Presentation consistent with ACS and Q waves in ≥2 leads or positive cardiac bio-markers OR silent myocardial infarction, as detected by abnormal Q waves, was confirmed by a core laboratory</td>
<td>Death</td>
<td>6.2 years</td>
<td>No difference in survival with PCI v no PCI (adjusted HR 1.03, 95% CI 0.83 to 1.21, P=0.76)</td>
</tr>
<tr>
<td>JSAP 2008</td>
<td>1 or 2 vessel CAD</td>
<td>50% PCI</td>
<td>Risk factor modifying medication at the clinician’s discretion</td>
<td>384</td>
<td>New Q waves in ≥2 leads OR convincing history with ECG changes compatible with non-Q-wave infarction, and the serum activities of ≥2 cardiac enzymes were ≥2 × ULN</td>
<td>Death, ACS, stroke, and emergency hospitalization</td>
<td>3.3 years</td>
<td>Reduced rate of primary endpoint in PCI arm (driven by higher rate of unstable angina (HR 0.66, 95% CI 0.45 to 0.98, P=0.04))</td>
</tr>
<tr>
<td>BARI-2D 2009</td>
<td>Type 2 diabetes mellitus</td>
<td>16% CABG 34% PCI 50% no revascularization</td>
<td>Guideline directed MT (aiming HbA1c &lt;7.0%, LDL cholesterol &lt;2.6 mmol/L, blood pressure &lt;130/80)</td>
<td>2368</td>
<td>Doubling of cardiac biomarkers and evidence of ischemia by symptoms, ECG, or imaging</td>
<td>Death from any cause (Major secondary endpoint composite of death, myocardial infarction, and stroke)</td>
<td>5 years</td>
<td>No difference in primary or major secondary endpoints between revascularization and no revascularization (survival 88.3% and 87.8% respectively, P=0.97)</td>
</tr>
<tr>
<td>FAME 2 2012</td>
<td>1, 2, or 3 vessel CAD</td>
<td>50% PCI 50% no PCI</td>
<td>Aspirin, ACE inhibition, statins, ezetimibe</td>
<td>888</td>
<td>&lt;24 hours since randomization: CK-MB 10 × ULN OR CK-MB 5 × ULN AND one of: new Q waves, angiographic coronary occlusion, new myocardium loss on imaging</td>
<td>Death, myocardial infarction, or urgent revascularization</td>
<td>0.58 years</td>
<td>Reduced rate of the primary endpoint in PCI arm (HR 0.32, 95% CI 0.19 to 0.53, P=0.001)</td>
</tr>
</tbody>
</table>

(Continued)
2.2 years No difference in primary endpoint between Death or myocardial infarction initial invasive or initial conservative arms (HR 1.01, 95% CI 0.79 to 1.29, P=0.95) Initial invasive arm had increased rate of death or dialysis initiation (HR 1.48, 95% CI 1.04 to 2.11, P=0.03) and stroke (3.76, 95% CI 1.52 to 9.32, P=0.004)

3.2 years No difference in primary endpoint between 777 Based on Third Universal Definition of myocardial infarction with higher biomarker thresholds for procedural myocardial infarction initial invasive or initial conservative arms (HR 0.93, 95% CI 0.80 to 1.08, P=0.34) Aspirin, statin, ACE inhibitors, ezetimibe

Table 1 | Continued

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</tr>
</thead>
<tbody>
<tr>
<td>FAME 2 Extended follow-up 2018</td>
<td>1, 2, or 3 vessel CAD 50% PCI 50% no PCI</td>
<td>Aspirin, ACE inhibition, statins, ezetimibe</td>
<td>888</td>
<td>As above</td>
<td>Death, myocardial infarction, or urgent revascularization</td>
<td>5 years</td>
<td>Reduced rate of the primary endpoint in the PCI arm (HR 0.46, 95% CI 0.34 to 0.63, P&lt;0.001). Endpoint driven by reduced rate of &quot;urgent revascularization&quot; in PCI arm (HR 0.27, 95% CI 0.18 to 0.41)</td>
<td></td>
</tr>
<tr>
<td>ISCHEMIA 2018</td>
<td>Moderate-to-severe ischemia 50% initial invasive strategy 50% initial conservative strategy</td>
<td>Aspirin, statin, ACE inhibition, ezetimibe</td>
<td>5179</td>
<td>Based on Third Universal Definition of myocardial infarction with higher biomarker thresholds for procedural myocardial infarction</td>
<td>Cardiovascular death, myocardial infarction, hospitalization for unstable angina, heart failure, resuscitated cardiac arrest</td>
<td>3.2 years</td>
<td>No difference in primary endpoint between initial invasive or initial conservative arms (HR 0.93, 95% CI 0.80 to 1.08, P=0.34)</td>
<td></td>
</tr>
<tr>
<td>ISCHEMIA -CKD 2018</td>
<td>Moderate-severe ischemia Advanced kidney disease 50% initial invasive strategy 50% initial conservative strategy</td>
<td>Aspirin, statin, ACE inhibitors, ezetimibe</td>
<td>777</td>
<td>Based on Third Universal Definition of myocardial infarction with higher biomarker thresholds for procedural myocardial infarction</td>
<td>Death or myocardial infarction</td>
<td>2.2 years</td>
<td>No difference in primary endpoint between initial invasive or initial conservative arms (HR 1.01, 95% CI 0.79 to 1.29, P=0.95)</td>
<td></td>
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</tbody>
</table>

Aspirin, ACE inhibitors, statins, ezetimibe

Follow-up of 3.2 years. 

CABG=coronary artery bypass graft; CAD=coronary artery disease; CI=confidence interval; CK=creatine kinase; ECG=electrocardiogram; FFR=fractional flow reserve; HR=hazard ratio; LAD=left anterior descending artery; LBBB=left bundle branch block; LM=left main stem; LVEF=left ventricular ejection fraction; MIB=miooglobin binding; MI=myocardial infarction; MTI=medical therapy; PCI=percutaneous coronary intervention; RRR=relative risk reduction; TIMI=thrombolysis in myocardial infarction; ULN=upper limit of normal.
general population, the presence of inducible ischemia is a powerful prognostic marker.\textsuperscript{36-39} Observational data have been used to recommend that revascularization is warranted when the amount of myocardium in which ischemia can be induced exceeds 10%. ISCHEMIA showed this reasoning to be sound. In a 2021 analysis, it showed that the anatomical CAD burden (judged on a 8 level scale) was a significant predictor of prognosis (P<0.05), but severity of ischemia was not.\textsuperscript{40} The driver for coronary events is therefore predominantly the amount of atheroma, rather than whether that atheroma is distributed in a way that elicits ischemia during testing.

Meta-analyses of RCTs

No trial is perfect, and every previous trial of revascularization has been subject to criticism (table 2). Meta-analyses are an attractive means to increase the sample size to have sufficient power to detect an effect size when the endpoint of interest (eg, death) is less frequent. However, these analyses are always subject to the selection criteria used for trial inclusion.\textsuperscript{41} For example, inserting trials of patients with recent un-revascularized myocardial infarction, such as the Swiss Interventional Study on Silent Ischemia Type II trial,\textsuperscript{42} generally sways the result in favor of the revascularization arm.\textsuperscript{43-44} However, when these trials are excluded, and only stable CAD patients remain, the result swings back with no benefit of revascularization.\textsuperscript{5}

Paradox explained

We now understand why medication has proved so effective in preventing death, while revascularization has not done so after the arrival of routine aspirin and statins. Medication works equally effectively along the entire coronary tree, whereas revascularization procedures focus on individual segments that are perceived as the most severe.

Revascularization by CABG provided survival benefits when it was not possible to slow down the degenerative atheromatous changes that led to plaque rupture, thrombotic vessel occlusion, and resulting myocardial infarction. But substantial advances in revascularization techniques have not translated into reduction of cardiovascular events. This is owing to parallel development in risk reduction medical therapy, which has the additional advantage of treating the totality of atherosclerotic disease, not simply the most angiographically severe lesions.

<table>
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<tr>
<th>Criticism</th>
<th>Examples of trials that received this criticism</th>
<th>Is that criticism fair?</th>
</tr>
</thead>
<tbody>
<tr>
<td>“The medical therapy in this therapy was too good and unrealistic”</td>
<td>COURAGE ORBITA ISCHEMIA</td>
<td>Disease modifying medical therapy such as statins reduces the risk of myocardial infarction and death in stable CAD. This should therefore be considered standard of care. The COURAGE trial was right to randomize patients established on good medical therapy. Medical anti-anginal therapy is safe, effective, and well tolerated in most patients with stable CAD. The incremental benefit of PCI on angina may be attenuated by the level of background medical therapy. PCI is associated with small but non-negligible short term and long term risks, and international guidelines would support establishing two anti-anginal agents as a minimum before referring patients for PCI. The impact of PCI on angina in the setting of real world anti-anginal therapy is the subject of the ongoing ORBITA-2 trial</td>
</tr>
<tr>
<td>“Medical therapy was too poor”</td>
<td>ACME FAME-2</td>
<td>Low levels of, and less potent medical therapy are more common in the earlier trials and reflect how practice has changed in the contemporary era. Consider how optimum medical therapy levels were when evaluating the results of trials</td>
</tr>
<tr>
<td>“The patients in the trial did not have enough ischemia”</td>
<td>RITA-2 MASS-II COURAGE</td>
<td>Ischemia is a distinct clinical entity that reflects an inability to match myocardial oxygen demand with coronary blood supply. It is measured using a variety of techniques that have evolved over time and vary with local practice. Some techniques, such as a treadmill exercise test, only speak to its presence or absence, while others, such as nuclear imaging, report ischemia quantitatively. Ischemia burden is known to correlate with adverse outcomes in clinical trials and observational studies. Historical trials did not routinely measure ischemia, focusing instead on anatomical disease severity (MASS-II, RITA-2). The prognostic implications of ischemia, when corrected for anatomic coronary disease severity, are uncertain. The recent findings of the ISCHEMIA trial, where even in the setting of moderate to severe ischemia, an early invasive strategy did not reduce the risk of myocardial infarction or death, has addressed this historical criticism of early trials</td>
</tr>
<tr>
<td>“Not enough proximal LAD”</td>
<td>ACME</td>
<td>This formed the basis for the rationale for MASS</td>
</tr>
<tr>
<td>“Only balloon angioplasty was performed”</td>
<td>MASS</td>
<td>The trial reflects the treatment strategy of the era. MASS-II was designed to counter this criticism</td>
</tr>
<tr>
<td>“Bare metal stents were used”</td>
<td>ACME MASS MASS-II</td>
<td>The trials reflect the treatment options available at the time. Newer trials have used drug eluting stents</td>
</tr>
<tr>
<td>“The chosen primary endpoint was incorrect”</td>
<td>ORBITA</td>
<td>Primary endpoints are chosen by study teams based on existing data and the objectives and aims of the trial, without knowledge of the results</td>
</tr>
<tr>
<td>“Unblinded designs should not be used for symptom assessment”</td>
<td>RITA-2 COURAGE FAME-2 ISCHEMIA</td>
<td>Blinded trials are complex and can be difficult to fund, conduct, and complete</td>
</tr>
<tr>
<td>“The patients did not have enough angina”</td>
<td>ORBITA ISCHEMIA</td>
<td>In ISCHEMIA, one third of patients had no angina, but the study was not designed to measure the impact on angina. ORBITA patients had a clinical diagnosis of angina and were referred for PCI on clinical grounds to improve their symptoms</td>
</tr>
</tbody>
</table>
Residual questions today
Necessarily, trials have strict inclusion criteria which mean they do not capture the full breadth of patients with stable CAD. Each trial builds upon the learnings of trials that went before. For example, COURAGE did not randomize patients before coronary angiography because in that era it would be considered too dangerous. ISCHEMIA was designed to address this limitation. Researchers were confident enough to not require invasive angiography, but did require a pre-randomization non-invasive computed tomography coronary angiogram solely to exclude left main stem stenosis. However, ISCHEMIA did hold back from randomizing some patients who were felt to be too high risk: patients with heart failure (left ventricular ejection fraction <35%), left main stem (LMS) stenosis, and “unacceptable” angina at baseline.

The trade-off of revascularization
Revascularization has an upfront “cost” to patients in the form of periprocedural risk, such as bleeding, stroke, myocardial infarction, and death. The intention is that this risk is worth while over the years to come through fewer subsequent events.

The day after revascularization, the event count is always much worse for revascularization than no revascularization. How quickly this initial investment by the patient pays off, in terms of reduced subsequent events, is the key question that all these trials have been trying to answer. It seems that the payoff is always further away than we believe when planning the trial. This is not because the procedure is more dangerous than we thought. Rather, it is because the subsequent events are fewer than we feared.

Does screening have a role?
With CAD now the leading cause of death not just in developed countries, but worldwide, and the availability of excellent preventive agents, should we screen for CAD? We suggest two reasons to be hesitant.

First, any screening program risks automatically funneling into revascularization because that has been our traditional practice when we assumed that coronary disease “required” revascularization. This is not only because of the habits of physicians. Patients, too, may understandably jump to the conclusion that narrowing occurs, it should be “fixed.”

Second, the lifetime risk of cardiovascular events is approximately one in three for men and one in four for women. This is already so high that the variation between individuals in their risk is a relatively small component in evaluating the net benefit of preventive therapy; far greater is the individual variation in their willingness to take preventive medication.

Revascularization for symptoms
Special considerations with symptom endpoints
Unlike medications, procedural interventions to reduce symptoms have largely been exempt from the gold standard requirement to be tested against placebo control. This means that most trials of symptom relief from procedural interventions are unblinded and therefore the reported therapeutic effect size is a mixture of the physiological and placebo effects.

Lack of survival benefit moves spotlight to symptoms
For several decades, the objective of trials of revascularization in stable CAD was to prove prognostic benefit. Whether they investigated single or multivessel disease, people with or without diabetes, or those with more or less ischemia, the trials had one factor in common: all were unblinded.

Unblinded design is perfectly acceptable if the endpoint is mortality. Unfortunately, when no impact was seen in mortality, authors and commentators placed increased focus on the observation of reduced angina. Numerous examples exist of this pattern occurring (table 3). RITA-2 was statistically significantly positive for increased death and myocardial infarction in the intervention group. However, discussion centered upon the unblinded observation of symptomatic relief.

Similarly, BARI-2D showed that neither PCI nor CABG improved prognosis. Nevertheless, patients who received revascularization reported less angina. Notably, this symptom relief was greatest in CABG versus no CABG stratum.

ISCHEMIA showed no difference between active and control in the five-component event endpoint. However, the report of the key secondary endpoints of health status outcomes gave cause for optimism. The invasive arm reported a significantly greater improvement in angina.

This is not an exhaustive list of unblinded trials of revascularization in stable CAD with neutral prognostic endpoints but positive symptomatic benefits. Numerous other examples exist. However, we must ask ourselves: what is the value of these results?

Symptom relief
The most powerful reduction of angina symptoms comes from telling a patient that their lesion is not causing a problem. The DEFER and FAME-2 landmark clinical trials validated the use of FFR to guide revascularization. The most striking, and poorly publicized results of these unblinded trials were that when the study physicians told patients that their FFR value was “negative” or their stenosis “non-significant,” a 39% relative risk reduction was seen in the number of patients reporting chest pain in DEFER, and a 77% relative risk reduction in CCS II-IV angina in FAME. This dramatic improvement was seen with no change to medical treatment, nor any attempt at revascularization. The simple act of telling the patient that the artery was unobstructed was enough to reassure the patient enough to markedly influence their symptoms.
No significant difference in SAQ summary score between revascularization and conservative strategies at 50% initial invasive strategy (PCI 85%, CABG 15%).

Significantly greater increase in SAQ summary score in the group randomized to revascularization (difference in increment of 4.1, 4.2, and 2.9 points at 3, 12, and 36 months, respectively). Balloon angioplasty reduced ≥CCS II angina by 16.5% (P=0.001) over conservative therapy. Exercise time increment of 35 s in favor of balloon angioplasty at 3 months (P=0.001).

Balloon angioplasty superior for angina freedom (62% v 47%, P=0.05), and exercise time increment (+79.8 s mean difference, 95%CI 6 to 144 s).

Angina freedom superior with either CABG (59%) or PCI (52%) in comparison with no revascularization (36%, P=0.001 and P=0.001, respectively). No significant difference between PCI and CABG (P=0.16). No patient had ≥CCS II angina in any group at follow-up. Significant reduction in rate of positive ETT following CABG (36%, P=0.001) or PCI (18%, P=0.005), but no revascularization group (5%, P=0.45).

Overall change in CCS class significantly better in the PCI+MT group (P<0.0001). Angina freedom from angiography at 10 year follow-up was 64% for CABG, 59% for PCI, and 43% with no revascularization. No patients had refractory angina in any arm.
The main treatments shown to be efficacious beyond this reliable placebo effect are pharmaceuticals, which cannot gain a license without blinded clinical trials. So powerful are these anti-anginal drugs that they are recommended as the primary strategy for management of patients with angina.

Outside cardiology, many procedures have undergone placebo controlled trials. Vertebroplasty was neutral,49 50 knee arthroscopy was neutral,51 and autologous blood injection was neutral.52 For angina, several surgical procedures have undergone placebo controlled trials. In the 1950s, hundreds of patients underwent internal mammary ligation, which caused a dramatic reduction in angina. Eventually, this underwent a placebo controlled trial, which revealed the ligation itself to be ineffective.53 All the previously reported benefit was placebo. So far, no placebo controlled trial of CABG has taken place to test for symptom relief.

Multiple unblinded trials consistently showed that laser myocardial revascularization was effective in relieving angina.54 55 It was only when a placebo controlled trial was conducted that the effect was recognized to be placebo.56

The Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial tested the incremental benefit of PCI compared with a placebo procedure on guideline recommended background anti-anginal drugs for the treatment of stable angina. Two other placebo controlled trials are ongoing.57 58 ORBITA in many respects mirrored a previous unblinded trial, the Angioplasty Compared to Medicine (ACME) trial, which similarly randomized 200 patients and reported an improvement in exercise time of 96 seconds.59 ORBITA was conservatively designed to be able to detect a between-group difference in treadmill exercise time increment of just 30 seconds, ie, even one third of the unblinded finding.

ORBITA enrolled patients with severe single vessel CAD and symptoms of angina. It found no significant improvement in treadmill exercise time beyond placebo. No significant difference was seen between PCI and placebo in angina status as assessed by CCS score or SAQ derived angina frequency. All of this was despite eliminating the anatomical obstruction and the ischemia seen on stress echo.60

Severity of ischemia, as assessed by invasive physiology, did not predict placebo controlled relief of angina. Severity of ischemia assessed by stress echo, however, did seem to predict placebo controlled angina relief, albeit weakly.61

However, this analysis showed only one symptom parameter in which PCI did seem to make a difference, in that one in five more patients in the PCI arm compared with the placebo arm were free from angina at follow-up.62 The ORBITA trial generated many questions. Retrospective analysis showed that one symptom parameter, namely achieving freedom from angina, did meet criteria for statistical significance. Was this a chance finding or a pointer to where important impact should be sought? Would effects be greater in multivessel disease? Would effects be greater with no background anti-anginal medication? Only 94% of ORBITA patients were known to have a positive ischemia test before randomization: would it be different if this were 100%? ORBITA-2 is tackling these questions.57

Experience with surgical and cardiological procedures has shown that it is safe and feasible to carry out placebo controlled trials for symptom relief, and trials without placebo control mislead us because the placebo component is not only larger than anyone suspects, but also surprisingly consistent.

CABG compared with PCI
Several trials have compared CABG with PCI, in patients technically suitable for both. These are not the focus of this review, but their results are summarized in table 4.

Special patient subgroups
Proximal LAD
If the hypothesized prognostic benefit of revascularization in stable CAD is prevention of myocardial infarction downstream of a vessel stenosis, then it is mechanistically plausible that the greatest benefit will come from treating the vessels which subtend the largest area of myocardium: the proximal left anterior descending artery (LAD) and the LMS. In early trials of revascularization some evidence supported this hypothesis. In the European Coronary Surgery Study from the 1970s, a non-significant trend was seen toward greater benefit with revascularization in patients with proximal LAD stenosis.23 The subsequent MASS trial recruited only patients with proximal LAD stenosis and found a significant reduction in the composite primary endpoint.28 However, this endpoint was driven entirely by “revascularization for angina,” which is of unclear significance in an unblinded trial. More contemporary trials of revascularization compared with a conservative approach have included large numbers of patients with a proximal LAD stenosis (34% in COURAGE and 47% in ISCHEMIA) and have not found prognostic benefit with revascularization.

Left main stem
LMS stenosis causes particular concern because acute occlusion here is usually promptly fatal. Surgical trials before the era of statins showed clear survival benefit of CABG in these patients. Subsequent trials of PCI53—even ISCHEMIA, which was buttressed by the favorable safety data from COURAGE—have not randomized patients with LMS disease between intervention and control.64 65

Studies of LMS have considered the choice between CABG and PCI. Several trials have found that the mortality outcomes are mostly similar, although the EXCEL and NOBLE trials indicated a survival advantage for CABG. What consistently differs between the therapies is the timing and nature of
other complications. With CABG the upfront risk of stroke is greater, whereas PCI has a higher rate of needing more revascularization in the years to come.66-68

Three vessel disease
The conventional belief that three vessel CAD is a high risk subset is informed by data from large registries, which showed worse prognosis in patients with three vessel CAD.66 It would be easy, therefore, to extrapolate this data to support the theory that revascularization of three vessel disease is required to improve mortality. Unfortunately, accepting such a simple inference falls into the trap of equating association with causation. Patients with three vessel disease are more likely to be older registries, which showed worse prognosis in patients with three vessel CAD.66 It would be easy, therefore, to extrapolate this data to support the theory that revascularization of three vessel disease is required to improve mortality. Unfortunately, accepting such a simple inference falls into the trap of equating association with causation. Patients with three vessel disease are more likely to be older
and have more comorbidities than those with one or two vessel disease.\textsuperscript{78} Despite the guidance that revascularization of stable three vessel disease with normal ejection fraction offers a survival benefit, the randomized data to support this are extremely limited, and from a previous era in which CABG was compared with now outdated medical therapy. The CASS study found no significant difference in 10-year survival between patients with angiographic three vessel disease randomized to an initial strategy of revascularization with CABG or medical therapy alone, though the results were more favorable for CABG in the subset of patients with left ventricular impairment.\textsuperscript{70}

With continuing technical improvements in PCI, and the advent of drug eluting stents, operators are increasingly able to treat more complex patterns of CAD with a lower risk of long term complications. Attention has therefore shifted toward the question of whether patients with three vessel disease are better served by CABG or PCI, which is beyond the scope of this review.

**Chronic total occlusions**

Chronic total occlusions (CTOs) illustrate the complex relationship between angina, ischemia, and coronary anatomy. Here, either progressive atherosclerotic narrowing or perhaps asymptomatic thrombotic occlusion leads to a patient presenting with a fully occluded vessel and no features of acute myocardial infarction. This may be diagnosed in a patient presenting with stable angina or even incidentally in an asymptomatic person. Often, effective collateralization has taken place through the process of angiogenesis in response to a chronic ischemic stimulus. With this collateralization, the myocardium subtended by a CTO is often found to be viable and may or may not be ischemic under stress. So far, despite multiple registries said to be favorable,\textsuperscript{71} randomized trials of revascularization of CTOs have shown no sign of survival advantage.\textsuperscript{72,73} The trials are generally unblinded and consistently report angina relief.\textsuperscript{74}

**Patient subsets**

**Diabetes**

In patients with diabetes, not only is the rate of progression of atherosclerosis higher, but the risk of re-stenosis inside a stent is also elevated. Perhaps for these reasons, revascularization and CABG may be of greater benefit in patients with diabetes than in the general CAD population. The Future Revascularization Evaluation in Patients with Diabetes Mellitus Optimal Management of Multivessel Disease (FREEDOM) trial randomized 1900 patients with diabetes and multivessel CAD to PCI or CABG. A significantly lower rate of the composite primary endpoint of death, myocardial infarction, and stroke with CABG was noted compared with PCI, driven by a substantially lower rate of myocardial infarction.\textsuperscript{75} BARI-2D showed a reduced rate of myocardial infarction with CABG over medical therapy alone.\textsuperscript{75}

However, the CARDIA trial did not find an advantage for revascularization and the ISCHEMIA trial had 42% patients with diabetes who showed no sign of benefit from early invasive therapy.\textsuperscript{75,76} In a pooled patient level meta-analysis of 5034 patients with diabetes, CABG in addition to medical therapy reduced the primary endpoint of death, myocardial infarction, and stroke compared with PCI in addition to medical therapy, and medical therapy alone.\textsuperscript{77}

In modern practice, many patients with diabetes and CAD are referred for revascularization. Where revascularization is chosen, CABG may be favored over PCI in the setting of diabetes and multivessel CAD, subject to a discussion by the cardiology team.

**Chronic kidney disease**

Cardiovascular mortality increases linearly as glomerular filtration rate falls.\textsuperscript{78} Patients with chronic kidney disease (CKD) who frequently present with stable CAD and a higher absolute risk of ACS are therefore particularly vulnerable. However, the question of whether elective revascularization offers net benefit in patients with CKD has eluded cardiologists because trials of revascularization have typically excluded\textsuperscript{79} or enrolled too few patients with CKD.\textsuperscript{30,34}

In the ISCHEMIA-CKD (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches Chronic Kidney Disease) 777 patients with moderate to severe ischemia and an eGFR $<30$ mL/min or hemodialysis dependence were randomized to an early invasive strategy or conservative therapy. At a median 2.2 years of follow-up, no significant reduction was seen in the incidence of the primary composite endpoint of death and myocardial infarction in the group randomized to the invasive strategy. Despite the unblinded nature of the trial, which may have favored the invasive strategy, no difference was seen between groups in the health status and quality of life outcomes. Importantly, a signal of harm was seen in the invasive group, with a higher incidence of stroke and death or new onset of dialysis.\textsuperscript{79}

**Pre-operative revascularization before non-cardiac surgery**

Perioperative myocardial infarction complicates approximately 5% of non-cardiac surgical procedures, and although many of these events are asymptomatic at the time of occurrence, they are associated with significantly increased mortality.\textsuperscript{80} Whether pre-emptive revascularization of coronary artery stenoses in patients undergoing non-cardiac surgery reduces cardiac risk has been a subject of controversy for several decades. The Coronary Artery Revascularization Prophylaxis (CARP) trial randomized patients at high risk for perioperative complications undergoing major vascular surgery to pre-operative revascularization or conservative management.\textsuperscript{81} No significant difference was found between groups in the incidence...
of perioperative myocardial infarction or death at long term follow-up. More recently, a smaller RCT found no significant difference between a strategy of pre-operative systematic versus selective coronary angiography on the incidence of in-hospital major adverse cardiac events, but did report improved survival and freedom from cardiovascular events at 4.8 years’ follow-up, in the group randomized to systematic coronary angiography.83 Finally, in a trial of patients undergoing carotid endarterectomy, systematic coronary angiography with possible follow-on PCI significantly reduced the incidence of postoperative myocardial infarction.84

The ill defined role for coronary revascularization before non-cardiac surgery is reflected in the latest consensus documents, which state no merit in adopting a strategy of systematically searching for “silent” ischemia in patients undergoing non-cardiac surgery.85

**Emerging treatments**

Despite five decades of PCI and CABG, evidence for their use for the treatment of angina is still emerging. While some trials are under way (table 5), many open questions remain, especially regarding how they can be used to relieve angina beyond placebo.

A novel angina procedure is the coronary sinus reducer (CSR). This is an hourglass shaped device implanted in the coronary sinus to generate a venous backpressure.86 This is hypothesized to have a number of different physiological effects, including the improvement of subendocardial myocardial perfusion, though the mechanism remains unclear.86 Unusually in the field of interventional cardiology, the CSR shows an improvement in angina compared with placebo. In the Coronary Sinus Reducer for Treatment of Refractory Angina trial, 104 participants with severe and refractory angina were randomized to CSR or a placebo procedure. Angina improved in a significantly higher proportion of participants with CSR than with placebo. Replication of this encouraging placebo controlled data, as well as mechanistic insights into the CSR, may lead to greater uptake of this treatment, and trials are ongoing.87

**Guidelines**

Guidelines take time to update with trial results, not least because guideline writers have to work within the legacy of previous guidelines.88 Various international societies have published best practice guidelines regarding revascularization in stable CAD. The ESC 2019 guidelines emphasize an initial approach with optimal medical therapy, with revascularization indicated as an additional therapy when symptoms are not satisfactorily controlled, referring to unblinded symptom relief with revascularization seen in numerous trials.8 However, interestingly, figure 1 of the 2019 ESC guideline on management of stable angina still sketches an

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Table 5 | Upcoming trials of revascularization

<table>
<thead>
<tr>
<th>Trial</th>
<th>Question</th>
<th>Design</th>
<th>Primary outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISCHEMIA Extended follow-up International study of comparative health effectiveness with medical and invasive approaches</td>
<td>To compare an early invasive strategy with a conservative strategy for patients with stable CAD and evidence of ischemia on prognostic endpoints at extended follow-up</td>
<td>Multicenter open label randomized controlled trial</td>
<td>Composite of cardiovascular death, MI, admission to hospital for unstable angina or heart failure or resuscitated cardiac arrest</td>
</tr>
<tr>
<td>ORBITA-2 A placebo controlled trial of percutaneous coronary intervention for the relief of stable angina</td>
<td>What is the placebo controlled benefit of PCI for patients with stable angina, single or multivessel CAD with evidence of ischemia, on real world anti-anginal therapy?</td>
<td>Multicenter, double-blind placebo controlled RCT</td>
<td>Change in angina symptom score between groups at 12 weeks</td>
</tr>
<tr>
<td>ORBITA-STAR Symptomatic trial of angina assessment prior to revascularization</td>
<td>Can placebo controlled symptom assessment during provoked ischemia predict symptomatic response from PCI?</td>
<td>Multicenter n-of-1 placebo controlled study</td>
<td>Angina reproducibility score correlated to reduction in angina episodes on smartphone app</td>
</tr>
<tr>
<td>ORBITA-COSMIC Coronary sinus reducer objective impact on symptoms, MRI ischemia and microvascular resistance</td>
<td>What is the mechanism of action of the CSR?</td>
<td>Multicenter, double blind, placebo controlled RCT</td>
<td>Difference in change in myocardial perfusion on MRI between CSR and placebo groups</td>
</tr>
<tr>
<td>IMAO Effect of permanent internal mammary artery occlusion on extracardiac coronary collateral supply</td>
<td>In the presence of a significant RCA stenosis, does catheter based occlusion of the right IMA improve collateral blood supply?</td>
<td>Open label, single arm clinical study</td>
<td>Change in right coronary collateral flow index</td>
</tr>
<tr>
<td>FAME-3 A comparison of fractional flow reserve-guided percutaneous coronary intervention and coronary artery bypass graft surgery in patients with multivessel coronary artery disease</td>
<td>Does FFR guided PCI in patients with multivessel stable CAD result in similar outcomes to CABG?</td>
<td>Multicenter open label RCT</td>
<td>Composite of death, MI, stroke, and any repeat revascularization at 1 year</td>
</tr>
<tr>
<td>SYNTAX-III REVOLUTION A randomized study investigating the use of CT scan and angiography of the heart to help the doctors decide which method is the best to improve blood supply to the heart in patients with complex coronary artery disease</td>
<td>Are treatment decisions for patients with complex CAD similar with coronary CT angiography in comparison to invasive coronary angiography?</td>
<td>Multicenter, all-comer, observational, cross-sectional study</td>
<td>Inter-rater agreement on revascularization strategy of two heart teams using an “Angio first” algorithm or a “CT first” algorithm</td>
</tr>
</tbody>
</table>

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**Notes**

- CABG=coronary artery bypass graft, CAD=coronary artery disease, CFI=collateral flow index, CSR=coronary sinus reducer, CT=computed tomography, FFR=fractional flow reserve, IMA=internal mammary artery, MI=myocardial infarction, PCI=percutaneous coronary intervention, RCA=right coronary artery, RCT=randomized controlled trial, SAQ=Seattle angina questionnaire.
STATE OF THE ART REVIEW

A 62 year old man presents with stable angina and is referred to the rapid access chest pain clinic. Computed tomography (CT) coronary angiogram, echocardiogram, and electrocardiogram (ECG) are ordered

VISIT 1
He is started on aspirin 75 mg, atorvastatin 40 mg and bisoprolol 5 mg
CT coronary angiogram: extensive calcification (1151 Agatston units)
Proceed to invasive diagnostic coronary angiography to evaluate coronary anatomy

VISIT 2
The angiogram shows a severe stenosis in the proximal left anterior descending artery (LAD) and his angina symptoms are ongoing. His case is discussed with the Heart team who feel medical therapy alone and percutaneous coronary intervention (PCI) with medical therapy are both options

The patient is started on amiodipine 5 mg once daily for further symptom relief and elects for medical therapy alone in the first instance with cardiology follow-up arranged

Visit 3
Patient is asymptomatic and a decision is made to continue with medical therapy

For the first six months the patient is asymptomatic. However, his angina recurs and after consultation with the GP he is started on further anti-anginal therapy with ranolazine 500 mg twice daily

Visit 4
ECG and echocardiogram are repeated and are unchanged. Following discussion with the patient, a decision is made to proceed with angiography and intravascular ultrasound guided PCI to the LAD

Fig 2 | Case study

80% reduction of event rate with revascularization and no tradeoff between an early excess event rate with intervention for gradual later benefit. Those guidelines also suggest revascularization when there is potential for “improvement in prognosis,” citing the FAME-2 5-year follow-up, in which improvement was seen with PCI in “urgent revascularization” and “spontaneous myocardial infarction” (though not total myocardial infarction).27

Guidelines from the National Institute for Health and Care Excellence (NICE, 2016) on stable angina similarly recommend an initial strategy of medical therapy, with revascularization reserved for those with ongoing symptoms. The guidelines have less of a focus on revascularization as a prognostic strategy, coming after the publication of both COURAGE and FAME-2. They emphasize risk reduction medication, with revascularization reserved for those with ongoing symptoms, and are careful not to presuppose a survival advantage of revascularization over medical therapy.89

NICE guidelines reference a “potential” survival advantage with CABG over medical therapy in patients with multivessel disease.89 They relate to the assessment and management of angina specifically and are best applied to a patient newly presenting with angina symptoms.

The American College of Cardiology (ACC, 2021) guidelines recommend revascularization for angina which persists despite medical therapy. Additionally, CABG is recommended to improve prognosis in the setting of LMS or multivessel CAD, with a class I level of evidence. PCI is recommended to improve prognosis in these patient groups, with lower levels of evidence.90 Despite their individual differences, guidelines uniformly recommend revascularization to relieve angina. Placebo controlled data are needed to inform this.

Conclusion
Over five decades since the introduction of revascularization for CAD, multiple studies have been conducted to understand the role of PCI and CABG in improving endpoints, including mortality, positivity, and quality of life.

QUESTIONS FOR FUTURE RESEARCH

- What is the placebo controlled impact of PCI on angina symptoms in patients with stable coronary artery disease taking the minimal tolerated anti-anginal therapy?
- Does revascularization reduce myocardial infarction or death in patients with left main stem stenosis when added to modern medical therapy?
- Does CABG reduce myocardial infarction or death in patients with three vessel coronary artery disease when added to modern medical therapy?
- Are any subsets of coronary artery lesions associated with worse long term outcomes?
- Which plaque characteristics are associated with worse long term outcomes and does revascularization modify these outcomes?
HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Our ORBITA patient focus group consists of six patients with lived experience of stable CAD and a placebo controlled trial of PCI. On trial exit, they were offered the opportunity to join the focus group with a view to facilitating ongoing public and patient participation and, ultimately, advancing the care of patients with stable CAD. Those patients are able to provide a rare perspective on shared decision making in stable CAD. They were all diagnosed with stable CAD in clinical practice and had often been offered PCI before volunteering to undertake the placebo controlled protocol of ORBITA. They offered their views on PCI for stable CAD, offering us contemporary, real-world opinions of patients with stable CAD. The preconceptions about stable CAD that emerge in the doctor-patient consultation were informed by this group, and their views helped us form the table Myths v Reality in the doctor-patient consultation (supplementary table).

rates of myocardial infarction, and symptoms of angina. Increasingly, the iterative studies and data have shown limited reductions in rates of myocardial infarction and mortality with revascularization, even in those patients with the highest burden of myocardial ischemia. Unblinded data have shown symptom improvement with revascularization, but the effect size was lower in the first blinded trial. Many questions remain unanswered, but clearly patients with stable CAD require aggressive risk factor modification with medical therapy, and this treatment has the greatest impact on their long term risk of myocardial infarction and death.

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Supplementary files supplied by the author

Table: Myths vs reality in the doctor patient consultation