

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Medical Therapy With Versus Without Revascularization in Stable Patients With Moderate and Severe Ischemia

The Case for Community Equipoise

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ABSTRACT

All patients with stable ischemic heart disease (SIHD) should be managed with guideline-directed medical therapy (GDMT), which reduces progression of atherosclerosis and prevents coronary thrombosis. Revascularization is also indicated in patients with SIHD and progressive or refractory symptoms, despite medical management. Whether a strategy of routine revascularization (with percutaneous coronary intervention or coronary artery bypass graft surgery as appropriate) plus GDMT reduces rates of death or myocardial infarction, or improves quality of life compared to an initial approach of GDMT alone in patients with substantial ischemia is uncertain. Opinions run strongly on both sides, and evidence may be used to support either approach. Careful review of the data demonstrates the limitations of our current knowledge, resulting in a state of community equipoise. The ongoing ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) is being performed to determine the optimal approach to managing patients with SIHD, moderate-to-severe ischemia, and symptoms that can be controlled medically. (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches [ISCHEMIA]; [NCT01471522](https://clinicaltrials.gov/ct2/show/study/NCT01471522)) (J Am Coll Cardiol 2016;67:81-99) © 2016 by the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS****ACS** = acute coronary syndrome**BMS** = bare-metal stent(s)**CABG** = coronary artery bypass graft**CAD** = coronary artery disease**CCTA** = coronary computed tomographic angiography**CI** = confidence interval**DES** = drug-eluting stent(s)**FFR** = fractional flow reserve**GDMT** = guideline-directed medical therapy**HR** = hazard ratio**LVEF** = left ventricular ejection fraction**MACE** = major adverse cardiac events**MI** = myocardial infarction**MT** = medical therapy**OMT** = optimal medical therapy**OR** = odds ratio**PCI** = percutaneous coronary intervention**QALY** = quality-adjusted life-year**QoL** = quality of life**RR** = risk ratio**SIHD** = stable ischemic heart disease**SPECT** = single-photon emission computed tomography

Patients with obstructive atherosclerotic coronary artery disease (CAD) may be asymptomatic (with or without ischemia), or present with symptoms ranging from stable angina, to acute coronary syndromes (ACS) (unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction), to sudden cardiac death. All patients with established CAD should be prescribed guideline-directed medical therapy (GDMT) to mitigate progression of atherosclerosis and to prevent myocardial infarction (MI) and cardiovascular death (1,2). In patients with biomarker-positive ACS, it is widely accepted that routine revascularization, in addition to GDMT, reduces the short- and long-term rates of death and MI compared with a more conservative approach (3-5). By contrast, the extent to which routine revascularization reduces death or MI, or improves quality of life (QoL) in patients with stable ischemic heart disease (SIHD) represents one of the greatest uncertainties in contemporary cardiology. Given that an estimated 15.5 million Americans have CAD, and that revascularization is performed in more than 1.3 million patients per year in the United States alone (6), the appropriate (but judicious) application of revascularization has enormous implications for the medical and economic health of the nation and the global community.

Early randomized trials of coronary artery bypass graft (CABG) surgery versus conservative care in patients with SIHD performed several decades ago suggested a survival benefit for CABG in patients with extensive anatomic disease, in whom a large amount of myocardium was at risk (left main disease, 3-vessel disease, and possibly 2-vessel disease involving the proximal left anterior descending coronary artery) (7). Ischemia on an exercise stress test also identified patients in whom mortality was reduced with CABG compared with medical therapy (MT) (7). These earlier randomized trials of CABG versus MT, however, antedated the more contemporary use of “disease-modifying” pharmacological interventions, including statins, inhibitors of the renin-angiotensin-aldosterone axis, and antiplatelet agents that individually have been shown to reduce death and MI in placebo-controlled trials. The aggregate use of such secondary prevention therapies, along with lifestyle interventions, such as cigarette

smoking cessation, diet, and regular exercise, has been referred to as optimal medical therapy (OMT), or GDMT (1,2).

More recently, the benefits of routine revascularization in SIHD have been questioned by the similar rates of death and MI observed in OMT-treated patients with and without percutaneous coronary intervention (PCI) in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, and with and without PCI or CABG in the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial (8,9). It may be argued that revascularization in SIHD may not be beneficial because not all anatomically obstructive coronary stenoses produce ischemia, or because not all high-grade coronary stenoses result in cardiac death and/or MI, or conversely, because most cases of cardiac death and/or MI arise from angiographically mild coronary lesions, which are not revascularized. However, some observational studies and hypothesis-generating substudy data from randomized trials suggest that the magnitude of ischemia is associated with adverse outcomes and that alleviation of ischemia may improve prognosis. Conversely, credible studies drawn from different (or even the same!) datasets have cast doubt on this premise. And importantly, often lost in this discussion is the extent to which revascularization improves QoL, a worthwhile goal, assuming noninferior rates of “hard” adverse event endpoints and reasonable cost-effectiveness.

Recent clinical practice guidelines from the United States and Europe, as well as U.S. appropriate use criteria, endorse GDMT for all patients with SIHD, but recommend (with variable levels of certainty) consideration of revascularization in patients with significant ischemia or symptoms that persist despite MT (10-14). Despite this uncertainty, highly enthusiastic proponents of both routine and selective revascularization for SIHD patients with ischemia may be found, and nearly everyone has an opinion. Indeed, attitudes run so strongly on this topic that it may be questioned whether clinical equipoise exists, although, when pushed, nearly all agree that definitive trials addressing the role of revascularization in optimally treated SIHD patients with substantial ischemia have not yet been performed.

The purpose of this review is to describe the evidence supporting the initial strategies of routine revascularization plus GDMT versus GDMT alone, with revascularization reserved for MT failure

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