ABSTRACT

Ischemic heart disease is the number one cause of mortality in both genders. Despite substantial gains in reducing mortality from cardiovascular disease, its prevalence is on the rise. Although percutaneous coronary revascularization procedures revolutionized the approach to acute coronary artery disease (CAD), their role in stable, chronic disease is less defined. As many more patients live on with stable forms of CAD, it is imperative that practitioners understand current evidence for and against revascularization, and develop a holistic, integrative approach to CAD. We examine current knowledge guiding decision-making in chronic CAD, and expand upon potential use of integrative approaches to chronic CAD.

Keywords: Heart disease; Stents; ISCHEMIA trial; Integrative cardiology
THE OPEN-ARTERY HYPOTHESIS

The advent of coronary artery stenting ushered in an exciting era of percutaneous coronary intervention (PCI) for treatment of acute and chronic coronary artery disease. However, before PCI became a common treatment, cardiology traversed decades of alternating hypothesis, animal experiments, and landmark trials to get to the state-of-the-art therapy we take for granted today. In the 1970s, the mere notion that coronary thrombosis is the cause of myocardial damage was controversial. The earlier attempts at angiography in acute myocardial infarction led to the observation of the coronary thrombus as the main culprit associated with myocardial damage. This led to the idea of the “clot busters” drugs, and their successful use to achieve coronary re-perfusion in acute coronary syndromes in the 1980s. Ushering in the era of thrombolysis in the treatment of acute myocardial infarction, the GISSI-1 (First Study of the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico), conducted in 1986, was the first major trial to prove that thrombolytic therapy with streptokinase improved survival.1 The largest randomized reperfusion study, GUSTO-I (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries), in 1993, demonstrated a 15% reduction in mortality with successful reperfusion at 90 minutes (which is now considered optimal “door-to-needle” time).2 These trials gave impetus to targeted therapies aimed at coronary plaque. In the next decade, following landmark reperfusion trials, primary percutaneous balloon angioplasty, coupled with intra-coronary stenting, including newer, drug-eluting stents, improved substantially over thrombolytic approach, with less side-effects, greater vessel patency, and lower cardiovascular mortality.

Although the benefit of PCI, first plain balloon angioplasty, and later intracoronary stenting, was quickly shown for acute coronary syndromes, such as ST-elevation myocardial infarctions, the role of PCI in stable ischemic heart disease (SIHD) was less defined. Unlike in acute coronary artery disease (CAD), observational studies failed to provide a definitive answer as to whether an invasive approach, including PCI or coronary artery bypass grafting (CABG), improved survival by reducing myocardial death, or prevented myocardial infarction when provided to stable patients already receiving state-of-the-art optimal medical therapy (OMT). Thus, the entire premise of the open-artery hypothesis, so significant in acute CAD, did not fit well into the treatment spectrum in SIHD. As the mortality due to acute CAD improved, in large part due to primary PCI in a setting of acute myocardial infarction, it became evident that the prevalence of coronary disease continues to rise. Thus, the essential question of “to stent or not to stent” forced the cardiology community to examine if invasive approaches meaningfully improved upon medical therapy, especially in those patients who demonstrated evidence of residual or chronic disease, as defined by findings of substantial coronary ischemia.1,3

ISCHEMIA-GUIDED REVASCULARIZATION STRATEGY

Previous studies, mostly observational, failed to provide a definitive answer to the dilemma of the open-artery hypothesis in patients with SIHD. These studies were limited and underpowered, and did not systematically evaluate patients for residual coronary artery disease, or ischemic burden.3,4 In addition, as both the medical therapy and invasive treatments advanced, the older studies no longer reflected contemporary practice, shaped by relentless technological advances in both medical therapy and invasive techniques.3

Resolving this issue became a key objective in optimizing patient management.1 Substantial resources are required to provide invasive treatments, and those are associated with risks as well as with benefits. Additionally, while OMT always included statins, some of the recent data shed doubts on the cholesterol hypothesis, and identified significant side-effects as well as adverse effects associated with those medications. This reconceptualization came amidst several pharma companies developing a novel class of cholesterol drugs, injectable proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which lack adverse effects associated with HMG-CoA reductase inhibition but are known for neurological effects,
and high cost. PCSK9 is an enzyme that binds to low-density lipoprotein (LDL) receptors, which stops LDL being removed from the blood, leading to an increase in blood levels of LDL. Inhibition of the enzyme leads to significant decreases in LDL cholesterol. Currently, unlike statins, no outcome data are available for PCSK9 inhibitors. Thus, to define the role of revascularization and OMT, and possibly re-define the nature of OMT in patients with SIHD, became one of the top 100 priorities for comparative effectiveness research identified by the National Academy of Medicine.5,6

The concept of ischemia-guided revascularization for SIHD emerged from an observational study of 10,627 consecutive patients, with no known CAD, who underwent assessment of residual coronary artery disease by measurement of ischemia using myocardial perfusion scintigraphy (1991–1997, Cedars-Sinai Medical Center, Los Angeles, CA).7 After a mean follow-up of 1.9 years, patients with moderate-to-severe ischemia (defined as >10% of ischemic myocardium on perfusion scintigraphy) demonstrated a significant reduction in cardiac deaths with early revascularization as compared with those receiving only medical therapy (not standardized or clearly defined), while those with no or mild ischemia had a survival advantage with medical therapy and not with revascularization.

However, two pivotal contemporaneous trials – the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) – performed in a random-ized, controlled fashion, spanning nearly 5 years, and rigorously controlled for types of OMT as well as providing lifestyle modification, failed to show any significant differences in total and cardiac mortality, or any reduction in the risk of major cardiovascular events for SIHD patients receiving invasive treatment and OMT versus those who received OMT alone.8,9 An extended follow-up of COURAGE (median follow-up: 11.9 years) yielded survival data that were consistent with the findings of the original trial report.10

The robustness of these findings, counterintuitive to many in the cardiology community, and contradictory to the established patterns of care, was questioned. The COURAGE trial was criticized because of a high rate of crossover from OMT to PCI, lack of using drug-eluting stents (they became available by the trial’s end), and an inability to control against selection bias due to reluctance of physicians to allow patients with high-risk coronary anatomy to enter the trial. As a result, only approximately 30% of patients showed greater than 10% myocardial ischemia, making it difficult to generalize results to a larger population group.8

**ISCHEMIA TRIAL AIMS TO REDEFINE ROLES OF PCI AND OMT**

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial is funded by NHLBI to define the value of revascularization in SIHD for patients with moderate-to-severe ischemia. ISCHEMIA is an international, randomized, controlled study, with a target enrollment of about 8000 patients with at least moderate ischemia on stress imaging and left ventricular ejection fraction of at least 35%.4 This trial overcomes the limitations of previous trials by randomizing patients to either a routine invasive approach of cardiac catheterization followed by complete revascularization and OMT, or OMT alone, with invasive strategy reserved for those patients who fail medical therapy. ISCHEMIA’s primary aim is to resolve whether the invasive strategy will reduce cardiovascular death or nonfatal myocardial infarction (over a follow-up period of 1.5–6 years) compared with the conservative strategy.4 To date, 3000 participants worldwide have been randomized. (For more, go to https://www.ischemiatrial.org.)

ISCHEMIA is deliberately structured to enroll patients after stress testing but before angiography, to avoid selection bias related to high-risk coronary anatomy.8 It utilizes modern imaging technology, such as coronary computed tomography angiography, to exclude significant left main coronary artery disease and confirm obstructive coronary artery disease prior to randomization. Invasive approach is used only for patients who fail OMT, and most advanced techniques are used to assess intermediate grade stenosis as well as provide access to contemporary stents (drug-eluting).
The ISCHEMIA study so far primarily recruited majority of the patients at the international sites, highlighting existence of a referral bias associated with findings of moderate to severe myocardial ischemia on the perfusion scintigraphy. However, a survey performed by ISCHEMIA trialists determined that that up to 80% of referring cardiologists would be willing to enroll SIHD patients with moderate-to-severe ischemia into a study like ISCHEMIA.  

ROLE OF INTEGRATIVE CARDIAC APPROACH IN SIHD

CAD takes decades to develop, and starts early in life. Inflammation triggers subsequent events occurring at the endothelial lining, all culminating in progression toward irreversible coronary stenosis, representing end-stage of CAD. Thus, lifestyle modification, aimed at control of vascular inflammation, is an early intervention that is likely to stop progression of CAD. Lifestyle modification strategy is included in both arms of the ISCHEMIA trial, opening the door to a possibility to explore its impact as part of OMT on major cardiovascular outcomes. Recently, a series of guidelines from the American College of Cardiology (2013) further reformulated our approach to identifying cardiac risk, and aided in deciding on the initiation and type of OMT (specifically, statins). For the first time, the newly released guidelines identified lifestyle effort as an initial strategy aimed at risk reduction. The ACC/AHA Guideline on Lifestyle Management to Reduce Cardiac Risk, while still reflecting established cholesterol and saturated fat paradigms, is nevertheless an important initial step in developing integrative strategies for patients with SIHD.  

Specifically, the guideline identifies gaps in our understanding, stating that “additional research is needed on the following topics related to diet: interaction between dietary modification and statin treatment; relative effects of saturated fats, monounsaturated fatty acids, polyunsaturated fatty acids, trans fatty acids, omega-3 fatty acids, and types of carbohydrates on lipids, inflammation, microbiome, and other newer potential CVD risk factors.”  

In summary, although the open-artery hypothesis revolutionized our approach to acute CAD, its role in SIHD is much less defined. A large scale NIH trial, ISCHEMIA, aims to definitively answer if ischemia-guided revascularization is of value in SIHD, on the background of OMT. The integrative approach is a promising strategy to the management of patients with SIHD.

CLINICAL TRIAL REGISTRATION

This article is based on the NIH-funded ISCHEMIA Trial (NCT01471522).

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DISCLOSURE OF INTERESTS

The author has nothing to disclose.

REFERENCES


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