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Viewpoint

The vast majority of the over 18 million Americans with known coronary atherosclerosis have stable disease (i.e., they do not have nor have they recently had an acute infarction or unstable angina) (1). Two management goals in this stable group have remained the same for over 50 years: to decrease angina symptoms if any are present and to decrease the likelihood of a subsequent myocardial infarction or cardiac death. Regarding the first goal, it is fairly easy to identify those experiencing symptoms and assess the relative benefits of interventions. The second goal, to identify those at increased risk for transitioning to unstable disease and to favorably alter that risk, is more uncertain. Our understanding of the pathophysiology and the implications of that understanding, in terms of management, have shifted over the years — a change that was accelerated by the results of the ISCHEMIA trial presented by Dr. Judith Hochman at the American Heart Association Scientific Sessions in November 2019 (2). An evolving view of disease management The responsible mechanism for stable, stress-induced symptomatic angina or ischemia, an oxygen supply/demand imbalance caused by a hemodynamically significant stenosis limiting supply, differs from that usually responsible for the transition to an unstable, acute coronary syndrome, which typically results from plaque rupture or erosion of a lesion of any degree of stenosis (3). [...]

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The vast majority of the over 18 million Americans with known coronary atherosclerosis have stable disease (i.e., they do not have nor have they recently had an acute infarction or unstable angina) (1). Two management goals in this stable group have remained the same for over 50 years: to decrease angina symptoms if any are present and to decrease the likelihood of a subsequent myocardial infarction or cardiac death. Regarding the first goal, it is fairly easy to identify those experiencing symptoms and assess the relative benefits of interventions. The second goal, to identify those at increased risk for transitioning to unstable disease and to favorably alter that risk, is more uncertain. Our understanding of the pathophysiology and the implications of that understanding, in terms of management, have shifted over the years — a change that was accelerated by the results of the ISCHEMIA trial presented by Dr. Judith Hochman at the American Heart Association Scientific Sessions in November 2019 (2).

An evolving view of disease management

The responsible mechanism for stable, stress-induced symptomatic angina or ischemia, an oxygen supply/demand imbalance caused by a hemodynamically significant stenosis limiting supply, differs from that usually responsible for the transition to an unstable, acute coronary syndrome, which typically results from plaque rupture or erosion of a lesion of any degree of stenosis (3). The emphasis on the presence, location, severity, and number of major coronary arteries with fixed disease, and using that information to inform the survival benefit of revascularization in patients with stable ischemic disease, was highlighted following the introduction and widespread use of coronary artery bypass surgery in the 1960s. There were three

large, randomized studies and a registry comparing surgery and medical therapies in these patients (4–6), all of whom underwent initial coronary angiography. The results differed, with some dependence on the length of follow-up and associated conditions, but were basically interpreted as indicating that surgery was preferred for symptom relief, for those with greater than 50% left main or greater than 70% disease in all three major coronary arteries with impaired LV function, and in some instances, for those with proximal left anterior descending (LAD) disease with impaired function. Subset analyses indicated that exercise-induced ischemia was also a predictor of acute myocardial infarction or cardiac death, which could be lowered with revascularization (7). This concept was also supported by a subsequent study evaluating the impact of stress-induced ischemia, as assessed by perfusion imaging in patients without a history of prior infarction (8). Thus, the number of diseased vessels and the location of disease, which could only be determined with angiography, were critical factors in assessing the future risk of infarction or cardiac death, and these data would importantly inform the value of surgical revascularization.

The lower complication rate with coronary angioplasty (percutaneous coronary intervention; PCI) and the demonstrated survival value of the procedure in patients with unstable disease (9) led to its widespread use in symptomatic, but also in asymptomatic, patients with stable disease. In the mid-2000s, the majority of angioplasty procedures performed in the United States were in patients with stable disease, with the goal of reducing subsequent cardiac events, despite the absence of large studies demonstrating a benefit in terms of infarction risk or survival (10). The most important study at that time was the Clinical Outcomes Utilizing Revas-

cularization and Aggressive Drug Evaluation (COURAGE) trial, which compared an invasive strategy consisting of PCI and optimal medical therapy (OMT) with OMT alone in 2287 patients with stable coronary disease, objective evidence of myocardial ischemia, and stenosis of at least 70% in at least one proximal epicardial coronary artery (11). Drug-eluting stents were placed in fewer than 3% of those in the angioplasty group, and the goals of OMT included an LDL-cholesterol (LDL-C) of lower than 85 mg/dL. There was a decrease in angina symptoms and a need for revascularization in the angioplasty group, but there was no difference in the death or nonfatal infarction rates — 19.0% and 18.5% in the PCI plus OMT and the OMT alone groups, respectively — at 4.6 years.

A modern look at an old problem

During the more than 15 years since the conduct of the COURAGE trial, the evaluation and management of coronary disease continued to evolve, and our assessment of the risk of transitioning from stable to unstable ischemic disease shifted from the importance of what has been termed hemodynamically significant stenoses, even as defined using fractional flow reserve (12), to total atherosclerotic burden, which can be assessed noninvasively with coronary calcium scoring (13, 14). At the same time, invasive and medical therapies for stable disease significantly improved with the use of drug-eluting stents, better antithrombotic regimens, and more aggressive lipid-lowering therapies and goals.

Thus, the stage was set then for the ISCHEMIA trial, addressing the same questions in the current era (2). Dr. Hochman and her collaborators studied, in stable patients with moderate or severe ischemia on a stress test, whether there was a benefit of performing coronary angiography and, if feasible, revascularization with angioplasty or bypass surgery, over and above that of prescribed OMT (15). All

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patients underwent an initial coronary CT angiogram to exclude those with unprotected left main coronary disease. The decision of whether the participant was experiencing moderate or severe ischemia was made at each site and determined by nuclear, echo, or magnetic resonance imaging or by exercise tolerance testing. The latter criterion was ≥ 1.5 -mm ST depression in two or more leads or 2-mm or more ST depression in a single lead at < 7 metabolic equivalents (METs), with angina. In addition to left main disease, those with Class III or Class IV New York Heart Association heart failure symptoms, impaired left ventricular function defined as an ejection fraction of less than 35%, acute coronary syndrome within the prior two months, or revascularization within the prior year were excluded. Those with severe kidney dysfunction were enrolled in the parallel ISCHEMIA-CKD study (16).

Of 8518 patients evaluated, 5179 were enrolled in the ISCHEMIA trial. Baseline demographic and clinical characteristics were well balanced with LAD disease in 87% of those in both groups and proximal LAD disease present in 46% and 47% of the invasive and conservative groups, respectively (17). The goals of prescribed medical therapy, achievement of which did not differ in the two groups, were LDL-C less than 70 mg/dL and on a statin, which was achieved by 59% of participants at the last visit; systolic blood pressures less than 140 mmHg, achieved by 77%; aspirin or another antiplatelet agent, achieved by 97%; and not smoking, achieved by 90%. Only 41% achieved all of the enumerated goals. Revascularization was performed in 80% of those randomized to the invasive group and in 23% at four years in those randomized to the conservative group. The primary outcome was cardiovascular death, infarction, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest and did not differ, occurring in 13.8% of those randomized to the invasive group and 15.5% of those randomized to the conservative group at four years. Cardiovascular death or infarction outcomes also did not differ over the four years (11.7% in the invasive and 13.9% in the noninvasive groups), but the incidence lines crossed at approximately two years — higher in the invasive group, initially, and then lower after approximately two years.

Although total infarcts did not differ, the invasive group participants experienced significantly higher periprocedural infarcts and significantly lower spontaneous infarcts than did the conservative group. There were no differences in treatment effects related to diabetes, angina frequency, number of vessels with significant stenosis, or degree of baseline ischemia. Two substudies were also presented. The quality-of-life outcomes analysis reported significant durable improvements in angina control and quality of life, with the invasive strategy for participants with — but not in those without — angina at baseline (18). In addition, the ISCHEMIA-CKD trial showed that an invasive strategy was not superior to a conservative strategy in patients with advanced chronic kidney disease and moderate or severe ischemia (19).

Interpreting the results

The investigators should be congratulated for designing and conducting an exemplary trial coordinating more than 5000 patients at 320 sites in 37 countries. The principal results from the ISCHEMIA trial — that an initial invasive strategy reduces symptoms in those with angina, but not cardiovascular death or infarcts — will certainly influence the medical care of millions of patients with stable ischemic disease and should be included in discussions between these patients and their physicians. Death and myocardial infarction are objective and quantifiable outcomes. Symptoms are individualized and subjective; some patients tolerate them more easily than others, and for the latter, there is symptomatic improvement and no increased overall risk of an invasive approach. The results apply only to those with stable disease; the invasive approach is clearly preferred, when feasible, in patients with unstable, acute coronary syndromes (9). It is also critically important to obtain longer-term follow-up data in the two groups. One reason why there were no significant differences in the primary outcome could be that procedural infarcts were increased, whereas spontaneous infarcts were reduced, with the invasive strategy. A previous study showed that spontaneous development of an infarct unrelated to PCI is a powerful predictor of subsequent mortality, whereas periprocedural infarcts are markers of baseline risk,

atherosclerosis burden, and procedural complexity; however, in most cases, they do not have independent prognostic significance (20). More detailed information regarding the stress test results, including the stage at which ischemia occurred and the presence of any stress-associated arrhythmias, may have longer-term prognostic value.

A comparison of the death/infarction rates in the COURAGE (19.0% and 18.5% in the invasive and conservative groups, respectively) and ISCHEMIA (11.7% and 13.9% in the invasive and conservative groups, respectively) studies indicate the progress made in both the invasive and conservative approaches to the management of patients with stable ischemic disease. Longer follow-up with more outcomes in both groups may include additional assessments as to whether there are — or are not — group differences, as a low event rate makes it more challenging to detect differences between the two tested strategies.

Going forward, it is important to recognize that coronary disease and its consequences remain the leading causes of premature death and lifelong disability in most countries (21). The difficulty of actually achieving OMT is illustrated by only a 41% success rate for all parameters in the ISCHEMIA subjects, despite their motivated participation in a clinical trial with the resources to faithfully explain and frequently monitor adherence. Strategies like a polypill approach (22) and longer-acting lipid-lowering therapies (23) may help to bridge this gap. In addition, the contributions of residual risk related to inflammatory, thrombotic, and metabolic factors continue to be explored (24). Understanding the underlying mechanisms for these and effective interventions are needed to further improve outcomes for our stable patients with atherosclerosis.

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