EDITORIALS

Managing Stable Ischemic Heart Disease

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The preferred contemporary approach to the management of stable ischemic heart disease, also referred to as chronic coronary syndrome,[1] is not well defined. Two strategies are commonly used.[2] The conservative strategy uses guideline-based medical therapy, including antianginal drugs as well as disease-modifying agents, such as hypolipidemic, antithrombotic, and renin–angiotensin blocking therapies. The invasive strategy adds coronary angiography, followed by either percutaneous coronary intervention or coronary-artery bypass grafting, to guideline-based medical therapy. Important advances have occurred in both strategies, leading to equipoise as to which approach is preferable for patients with stable ischemic heart disease.[3,4]

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA), the results of which are now reported in the *Journal*, tested whether an initial invasive strategy would result in better outcomes than a conservative strategy among patients with stable ischemic heart disease and moderate or severe myocardial ischemia. In the main trial, 5179 patients underwent randomization at 320 centers in 37 countries.[5] Another 777 patients who had advanced chronic kidney disease in addition to the other conditions were included in a separate trial (ISCHEMIA-CKD).[6] Both trials used a patient-centric approach by incorporating sophisticated analyses of angina-related quality of life.[7,8]

These trials have a number of important positive features. More patients underwent randomization in each trial than in previous trials addressing this issue. The patients had, on average, excellent control of low-density–lipoprotein cholesterol and systolic blood pressure, as well as glycated hemoglobin in those with diabetes.[5,9] The presence of moderate or severe ischemia was determined with stress imaging in the majority of patients. In ISCHEMIA, the majority of patients also underwent coronary computed tomographic angiography at screening to confirm the presence of coronary obstruction and to rule out left main coronary artery disease; the results of the imaging studies were confirmed on blinded review at core laboratories. Unlike in previous trials, randomization to the conservative and invasive strategies in these trials was carried out before coronary angiography was performed, thereby reducing the likelihood of bias.

In ISCHEMIA, 96% of the patients in the invasive-strategy group underwent coronary angiography, whereas only 26% of the patients in the conservative-strategy group did so, for an ischemic event or inadequate control of symptoms. The corresponding percentages in ISCHEMIA-CKD were 85% and 32%. Of note, in ISCHEMIA-CKD, half the patients in the invasive-strategy group did not undergo revascularization, most often because they did not have obstructive coronary disease, despite having a positive stress test. In the two trials, the power was reduced because enrollments and aggregated event rates were lower than anticipated, leading to changes in the planned sample sizes and, in ISCHEMIA, to a change in the primary end point.[10]

There was no significant difference between the two strategies in the rate of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest (the primary end point in ISCHEMIA) or in the rate of death from any cause or myocardial infarction (the primary end point in ISCHEMIA-CKD).[5,6] In ISCHEMIA, rates of death from any cause were quite low, at approximately 6.4% at 4 years in both groups. In ISCHEMIA-CKD, death rates were higher, at approximately 27% at 3 years, again without a difference between the two groups. The most straightforward conclusion is that, insofar as "hard" end

points are concerned, the two strategies seem to have been equally efficacious in the two trials. In ISCHEMIA, the patients in the invasive-strategy group reported substantially fewer anginal symptoms than the patients in the conservative-strategy group,[7] although the magnitude of this benefit depended on angina frequency at baseline (and 35% had no angina at baseline). In ISCHEMIA-CKD, there was no benefit with regard to angina-related health status with the invasive strategy.[8]

Possible reasons for the lack of difference in "hard" outcomes in ISCHEMIA are the relatively low risk for clinical events among the trial patients and the potential effect of practice patterns that may have excluded more-symptomatic patients from the trial in countries with a low threshold for revascularization. Of note, in ISCHEMIA, the Kaplan–Meier curves showed a trend for a greater number of myocardial infarctions (predominantly procedural) in the invasive-strategy group than in the conservative-strategy group during the first 6 months of the trial, but as the trial proceeded, the curves crossed, and more myocardial infarctions (predominantly spontaneous) occurred in the conservative-strategy group. At 4 years, the cumulative incidence of death from cardiovascular causes or myocardial infarction (based on the primary definition) was higher in the conservative-strategy group than in the invasive-strategy group (13.9% vs. 11.7%). It is possible that ISCHEMIA ended before a substantial difference in favor of the invasive strategy emerged. Since it is unlikely that ISCHEMIA will be repeated, it is especially important to extend follow-up with the patients before contact with them is lost; additional events may enhance our understanding of the effect of the trajectory of the event curves and ascertain the durability of the benefit of an invasive strategy with regard to control of angina. It would also be helpful to develop a risk score for the trial patients in order to determine the outcomes at various levels of risk.[11]

As pointed out by the authors of ISCHEMIA, when myocardial infarction was analyzed according to a secondary definition (see the Supplementary Appendix, available with the full text of the article at NEJM.org), the number and pattern of myocardial infarctions differed, leading to results that favored the conservative strategy throughout follow-up. Both the primary and the secondary definitions of myocardial infarction were complex. Analyses of the prespecified but not yet reported end points of "complicated" and "large" myocardial infarctions would be of interest and potentially informative to the clinical community.

Although there is some uncertainty regarding the interpretation of the ISCHEMIA results — given that the difference in outcomes between the two strategies is driven by results for myocardial infarction, and those results depend on the definition used in the analysis — the invasive strategy does not appear to be associated with clinically meaningful differences in outcomes during 4 years of follow-up. This finding underscores the benefits of disease-modifying contemporary pharmacotherapy for coronary artery disease. Thus, provided there is strict adherence to guideline-based medical therapy, patients with stable ischemic heart disease who fit the profile of those in ISCHEMIA and do not have unacceptable levels of angina can be treated with an initial conservative strategy. However, an invasive strategy, which more effectively relieves symptoms of angina (especially in patients with frequent episodes[7]), is a reasonable approach at any point in time for symptom relief.

Among patients with stable ischemic heart disease who have advanced chronic kidney disease, the risk of clinical events is more than three times as high as the risk among those without chronic kidney disease, but an initial invasive strategy does not appear to reduce event rates or relieve angina symptoms for these patients.[6,8] Therefore, patients with stable ischemic heart disease and chronic kidney disease can usually be treated with a conservative strategy.[12]

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Physical Therapy before the Needle for Osteoarthritis of the Knee

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Clinical guidelines for the treatment of osteoarthritis of the knee emphasize education, exercise, and (if appropriate) weight loss, rather than the use of drugs or surgery.[1,2] However, a survey conducted in four European countries showed that these treatments were recommended to fewer than half the patients; stronger painkillers were recommended in 52% of patients, and 36% were referred for surgery.[3] Intraarticular glucocorticoid injections are commonly used to treat osteoarthritis of the knee, partly because they are easy to administer, they involve fewer visits than other treatments, and patient adherence is not an issue. But benefits may be short-lived, and adverse effects on the joint have been reported, including a small increase in loss of cartilage volume of uncertain clinical relevance.[4] In contrast, physical therapy, including exercise, is used less frequently than glucocorticoid injections, and although physical therapy requires patient participation and investment of time, it is noninvasive, has negligible adverse effects, and may have longer-lasting benefits than glucocorticoid injections.

Few trials have directly compared different treatments for osteoarthritis of the knee. In this issue of the *Journal*, Deyle and colleagues[5] report the results of a pragmatic, randomized, controlled trial conducted predominantly in one military hospital in the United States. A total of 156 outpatients with osteoarthritis of the knee were assigned to undergo physical therapy or to receive intraarticular glucocorticoid injections. Outcomes were assessed at 12 months. It was not possible to conceal treatment assignments from patients or providers, and placebo injections were not included in the trial design.

Over the 12-month trial period, patients in the physical therapy group attended a mean of 11.8 treatment visits (range, 4 to 22), at which they received manual physical therapy and instruction on home exercise. The glucocorticoid injection group received a mean of 2.6 injections (range, 1 to 4) of triamcinolone acetonide. The primary outcome was the total score on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; scores range from 0 to 240, with higher scores indicating worse pain, function, and stiffness). Patients in the physical therapy group had less pain and functional disability at 1 year than patients in the glucocorticoid injection group. Although the magnitude of the absolute between-group difference in total WOMAC score (18.8 points) was small, 8 of 78 patients (10.3%) in the physical therapy group, as compared with 20 of 78 (25.6%) in the glucocorticoid injection group, did not have an improvement from baseline of at least 12% (the minimal clinically important difference) in the WOMAC score. Secondary outcomes measuring functional tasks and patient assessment of improvement, as well as sensitivity analyses, were in the same direction as the primary outcome, with the results favoring physical therapy. The results of the trial contrast with recent recommendations from some medical and research societies against manual therapy for osteoarthritis of the knee.[1,2]

There are several issues regarding the trial that are worth considering. First, patients in the physical therapy group had considerably greater contact time with clinicians than patients in the glucocorticoid injection group. This may have accentuated placebo effects and the therapeutic