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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should patients with stable ischemic heart disease undergo revascularization?

A: The answer is less clear for these patients than for patients with acute coronary syndromes. In the latter group, percutaneous or surgical revascularization reduces the rates of morbidity and mortality, whereas in patients with stable ischemic heart disease, benefits may be limited to the improvement of angina. Certain markers and criteria may help us in this decision, and trials are ongoing.

Of importance, all patients with coronary artery disease should receive guideline-directed medical therapy as tolerated, regardless of whether they undergo revascularization.

MEDICAL THERAPY FOR ALL

In all the relevant trials, patients with stable ischemic heart disease in both the revascularization groups and the unrevascularized groups received guideline-directed medical therapy. Current guidelines[1] give class I recommendations (ie, treatment should be given) for:

- Lipid management
- Blood pressure management
- Physical activity
- Weight management
- Smoking cessation
- Antiplatelet therapy
- Beta-blockers for patients with normal left ventricular function after an acute coronary syndrome event, and for those with an ejection fraction of 40% or less
- Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers for patients who have hypertension, diabetes mellitus, a left ventricular ejection fraction of 40% or less, or chronic kidney disease
- Annual influenza vaccination
- Anti-ischemic medications (beta-blockers, calcium channel blockers, nitrates) for relief of symptoms.

REVASCULARIZATION FOR SOME?

Results of the studies outlined below will help in deciding when to use guideline-directed medical therapy alone or medical therapy plus revascularization.

COURAGE trial: No added benefit in patients at low risk

The findings of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), published in 2007, suggested that in select patients, percutaneous coronary intervention for stable coronary artery disease was no better than guideline-directed medical therapy alone for reducing the outcomes of death, myocardial infarction, or hospitalization for acute coronary syndrome.[2]

The benefit is much less clear for stable disease than for acute coronary syndromes

Of note, however, is that the 2,287 patients included in COURAGE were a low-risk subset of the more than 35,000 patients initially evaluated. The investigators reviewed the patients' coronary angiograms before enrollment, and thus many patients with complex or high-risk anatomy were likely excluded based on an a priori assessment of angiographic images.

Also, coronary stent technology has substantially improved since COURAGE (which primarily used bare-metal stents and early drug-eluting stents), and this brings into question whether the results are applicable to current patients.

Moreover, in subsequent substudies from COURAGE, revascularization significantly im-

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proved symptoms of angina and quality-of-life scores compared with medical therapy alone.[3,4]

Also important is that more than one-third of the patients in the medical therapy group crossed over to revascularization during the study, most often for worsening symptoms of angina.

Regardless of its limitations, COURAGE played an important role in delineating the use of guideline-directed medical therapy alone in certain low-risk patients and sparked debate about when and if to revascularize other patients.

BARI 2D trial: CABG may benefit those with diabetes

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, published in 2009, aimed to find out if revascularization in patients with stable ischemic heart disease and diabetes was beneficial compared with medical therapy alone.[5]

While it was not designed to directly compare percutaneous coronary intervention vs coronary artery bypass grafting (CABG), it did find that medical therapy plus CABG might reduce the rate of adverse cardiovascular events in this population compared with medical therapy alone or medical therapy plus percutaneous intervention.

As with COURAGE, however, the patients in the medical therapy group in BARI 2D also had a high rate of crossover to revascularization, primarily driven by worsening anginal symptoms.

All patients with coronary artery disease should receive guideline-directed medical therapy as tolerated

FREEDOM and the 2014 updated guideline

Based on the findings of BARI 2D and those of FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease),[6] the American College of Cardiology and American Heart Association updated their recommendations in 2014.[7] This focused update states that for patients with diabetes and multivessel coronary artery disease, if revascularization is likely to improve survival (for example, in three-vessel disease or complex two-vessel disease involving the proximal left anterior descending artery), then CABG should be performed if a left internal mammary artery graft can be anastomosed to the left anterior descending artery. Otherwise, percutaneous coronary intervention should be reserved for those patients with diabetes and high-risk or complex multivessel coronary artery disease who are not good surgical candidates.

FAME 2 trial: Fractional flow reserve as a guide

The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2 (FAME 2) trial,[8] published in 2012, evaluated whether clinical outcomes differ between patients who undergo percutaneous revascularization plus medical therapy and those who are treated with medical therapy alone, using fractional flow reserve as a means to determine which stenoses should be considered for intervention. Fractional flow reserve performed during invasive angiography determines the ratio of intracoronary pressure to aortic pressure using a wire advanced across a coronary obstruction.

FAME 2 found a markedly lower incidence of the primary composite end point of death, myocardial infarction, and urgent revascularization with randomization to percutaneous revascularization plus medical therapy compared with medical therapy only (4.3% vs 12.7%, $P = .001$) in patients with a fractional flow reserve less than 0.80 (considered a hemodynamically significant obstruction). The trial was stopped early because of the markedly different outcomes.

Of note, however, the reduction in adverse clinical outcomes was driven primarily by a reduction in urgent revascularizations in those treated with percutaneous coronary intervention in the revascularization arm. Regardless, using fractional flow reserve to guide whether obstructive coronary lesions should be treated with percutaneous coronary intervention has appropriately become a mainstay in interventional cardiology.

Stress testing

Noninvasive stress testing has played a role in helping to guide revascularization decisions in stable ischemic heart disease. In particular, revascularization in the setting of greater than 10% ischemia on perfusion imaging has been associated with a lower risk of cardiac death than in those who were revascularized with an ischemic burden less than 10%.[9]

A substudy of COURAGE found that percutaneous coronary intervention reduced ischemia to a greater degree than medical therapy alone on serial nuclear stress tests in patients with stable ischemic heart disease.[10] In this substudy, when both groups were combined, the investigators also found that there were fewer adverse events in those who had an overall reduction of ischemia regardless of treatment strategy.

ISCHEMIA: Revascularize those with ischemia?

While COURAGE, BARI 2D, and FAME 2 suggested that early revascularization for low-risk patients with coronary artery disease does not confer a benefit over medical treatment alone with regard to hard clinical end points, it remains unclear whether an early revascularization strategy is advantageous in patients with stable ischemic heart disease who have at least a moderate amount of ischemia on noninvasive stress testing.

The ongoing ISCHEMIA (International Study of Comparative Effectiveness With Medical and Invasive Approaches) trial will help to answer that question. In this study, 8,000 patients with stable angina and at least moderate ischemia on noninvasive stress testing are being randomized before coronary angiography either to guideline-directed medical therapy plus revascularization (percutaneous or surgical) or to medical therapy alone.[11] The ISCHEMIA study population reflects current practice more closely than the previous studies discussed above in its inclusion of fractional flow reserve and later-generation drug-eluting stents.

The results of ISCHEMIA will be an important piece of the puzzle to answer whether patients with stable ischemic heart disease benefit from revascularization in terms of cardiovascular mortality or myocardial infarction (the primary end point of the study).

Studies in additional subsets

It is important to recognize that there are additional subsets of patients with stable ischemic heart disease (those with multivessel disease, left main coronary disease, or low ejection fractions, for example) who have been studied to help determine when and how to perform revascularization. In addition, there are guidelines[12] for both interventional cardiologists and cardiac surgeons that help delineate which patients should undergo revascularization. While a complete review is beyond the scope of this discussion, three trials are worth mentioning:

The Coronary Artery Surgery Study (CASS)[13] revealed that revascularization in left main coronary artery disease is associated with lower mortality rates than medical therapy alone. This study, along with others, eventually led to recommendations for revascularization to be performed in all patients with significant left main coronary disease, regardless of symptoms or stress test findings.[14,15]

The Surgical Treatment for Ischemic Heart Failure (STICH) trial[16] found that patients with a low ejection fraction (< 35%) and ischemic heart disease had no difference in all-cause mortality rates when treated with CABG plus medical therapy compared with medical therapy alone (although the study's design has been heavily criticized).

The Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) study[17] found that CABG was associated with fewer adverse events in three-vessel coronary artery disease or complex left main coronary artery disease compared with percutaneous coronary intervention. The study used early-generation paclitaxel drug-eluting stents that are no longer used in contemporary practice. This study established the SYNTAX score, which is often used to help make revascularization decisions. A low SYNTAX score of 0 to 22 (meaning less-severe coronary artery disease) was associated with equivalent outcomes for both percutaneous coronary intervention and CABG. Thus, even if there is multivessel disease or left main disease, if the SYNTAX score is low, then percutaneous coronary intervention is an acceptable method for revascularization with similar results as for CABG.

A TEAM APPROACH

Due to the complexity of stable ischemic heart disease and the subtleties of managing these patients, a multidisciplinary "heart team" approach may be the best way to navigate treating stable ischemic heart disease via revascu-

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larization or with medical therapy alone. The heart team approach could take advantage of the particular expertise that the primary care physician, cardiologist, interventional cardiologist, and cardiac surgeon provide.

The upcoming results of studies such as the ISCHEMIA trial will help to provide additional guidance for these teams in long-term management of patients with stable ischemic heart disease.

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