EDITORIALS

Assessment of Stable Coronary Lesions

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In recent years, concerns have been raised about the appropriateness of performing percutaneous coronary intervention (PCI) in patients with stable coronary artery disease.[1] One objective measure that is used to assess the potential benefit of revascularization is fractional flow reserve (FFR). FFR measurements, which allow for accurate assessment of stenosis severity, are obtained during an interventional procedure, in which the drop in pressure is measured across the lesion at rest and again after pharmacologic induction of hyperemia to increase flow through the lesion. Multiple randomized trials have established that lesions with normal FFR measurements can be managed medically without an increase in the risk of ischemic events.[2-4]

Despite strong data in its favor, the use of FFR remains low. One major reason is that in order to induce a hyperemic state (which simulates exercise), a vasodilator such as adenosine is administered. Adenosine may cause bradycardia or heart block and result in termination of the procedure. Fear of this potential complication limits the use of FFR. Increased procedural time and cost associated with FFR, as well as patient discomfort from chest pain and dyspnea caused by adenosine, are also issues to be considered. An alternative measure that can be used to assess the hemodynamic severity of a lesion is the instantaneous wave-free ratio (iFR), which does not require the administration of a vasodilator but instead relies on the calculation of the translesional pressure gradient during diastole.

The results of two trials of FFR versus iFR, now reported in the *Journal*, provide clarity regarding the preferred method for invasive assessment of stenoses of ambiguous (intermediate) hemodynamic severity.[5,6] In both the DEFINE-FLAIR trial (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and the iFR-SWEDEHEART trial (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome), patients who had stenoses of intermediate severity on angiography were randomly assigned to undergo assessment with the use of either FFR or iFR.[5,6] Most of the patients had stable coronary artery disease. In patients who had an acute coronary syndrome, the culprit lesion was treated according to standard practice, and then any additional lesions of intermediate severity were assessed with the use of iFR or FFR. When the iFR of a lesion was higher than 0.89 or the FFR was higher than 0.80, revascularization was deferred.

In both trials, iFR was shown to be noninferior to FFR with respect to the 1-year risk of primary end-point events, which were a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization. The results of these two trials were remarkably concordant. In a meta-analysis of the primary end-point results in the two trials (crude risk ratio, 1.03; 95% confidence interval, 0.82 to 1.28), the upper limit of the 95% confidence interval falls within a range that would meet contemporary standards for noninferiority in large cardiovascular-outcomes trials of pharmacotherapies,[7] and the sample size and degree of certainty exceed the criteria typically set in the evaluation of medical devices.

In addition, several secondary outcomes favored iFR. The rate at which PCI was performed was lower, the duration of the procedure was

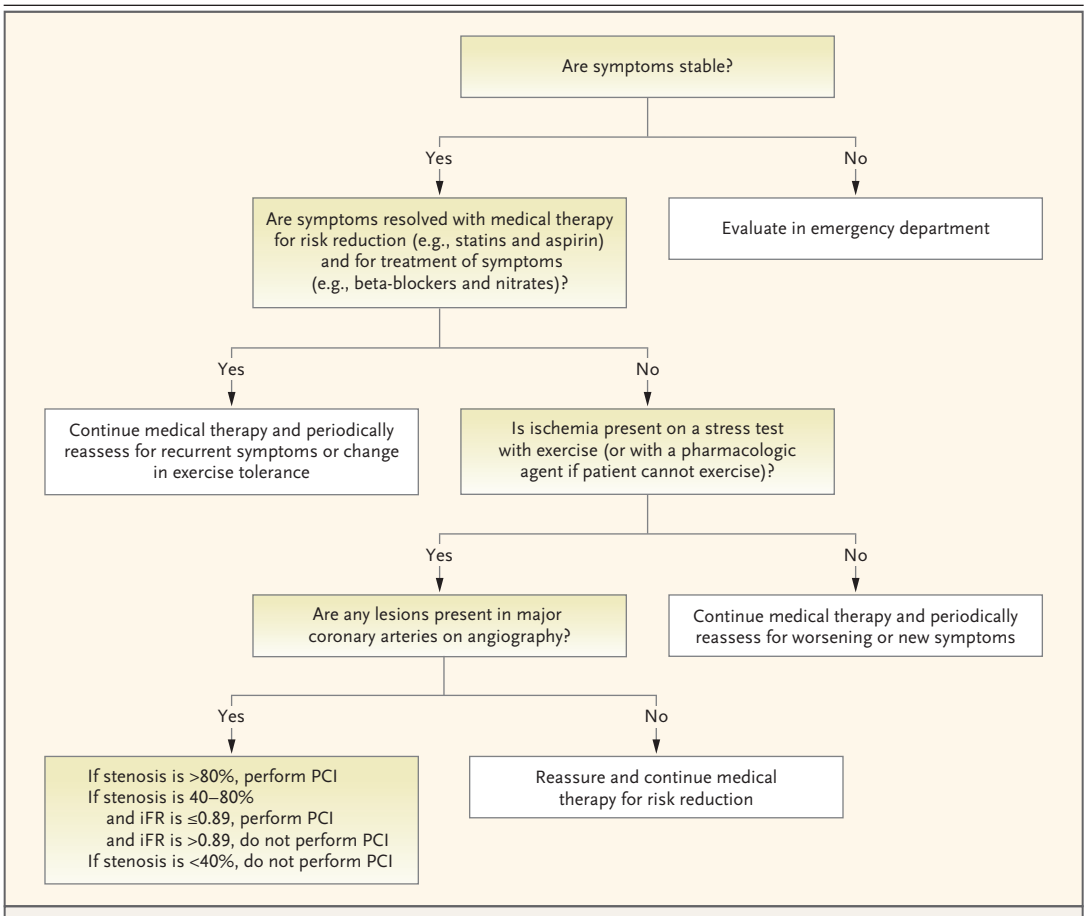

Figure 1. Evaluation of Stable Coronary Artery Disease.

When stable coronary artery disease is suspected, initial medical therapy, noninvasive evaluation, coronary angiography, and assessment with use of the instantaneous wave-free ratio (iFR) can be used to guide decisions regarding percutaneous coronary intervention (PCI).

shorter, and the percentage of patients who reported discomfort during the procedure was smaller in the iFR groups than in the FFR groups. These factors, as well as the lack of need for vasodilators, might be expected to lower health care costs, assuming that the price of the guidewire used for iFR measurement is not higher than the price of the guidewire used for FFR measurement. Another potential advantage of iFR is that it may help in the evaluation of serial lesions, which is a challenge with the use of FFR.[8] However, these issues were not addressed in these two reports, and further study is needed. The use of iFR might facilitate multivessel evaluation, which is viewed unfavorably by many operators who obtain FFR measurements because it results in a longer procedure and the need for repeat administration of adenosine.

In the treatment of stable coronary lesions, PCI is performed primarily for control of angina, and the use of iFR could help to guide decisions regarding PCI more rationally (Fig. 1). It is important to note that the results of these two trials do not apply to the evaluation of presumed culprit lesions in patients with acute coronary syndromes; for such lesions, current evidence favors early catheterization and revascularization guided by an anatomical assessment of lesion severity.[9,10] In the future, it would be an advance if noninvasive methods that provide simultaneous anatomical and physiological assessment of coronary lesions could supplant the need for invasive angiography. Nevertheless, there will always be patients in the catheterization laboratory who have a coronary stenosis of intermediate severity on angiography. FFR has been the

evidence-based standard for invasive evaluation of such lesions, but it now appears that iFR may be the new standard.

A statistical consultant for the *Journal* performed the meta-analysis of the two trials discussed in the editorial.

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New Lessons about Endometriosis — Somatic Mutations and Disease Heterogeneity

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Endometriosis is a common estrogen-dependent inflammatory disorder that affects 6 to 10% of women of reproductive age and up to 50% of women with infertility and pelvic pain.[1] Endometriosis is a complex disease with risk influenced by many factors; its pathogenesis is poorly understood, and current treatments have limitations.[2] A role for genetics is well established, with approximately 50% of risk due to genetic factors and 50% due to environmental or other causes.[3] The disease is heterogeneous, with multiple ectopic lesions containing endometrial-like tissue outside the uterus, primarily in the pelvic cavity.[1] The lesions may be one of three types: superficial peritoneal lesions, ovarian endometriomas, or deep infiltrating endometriosis. Histologic analysis of the lesions suggests that endometriosis is benign, but it shares features of cancer because lesions attach and invade other tissues. Symptoms of pain and infertility do not correlate well with the appearance of lesions, although pain correlates well with deep infiltrating disease. Histologic appearance and response to treatment vary according to lesion site, with more undifferentiated endometriosis in areas of deep infiltrating endometriosis.[4] The heterogeneity of lesions, disease course, and symptoms raises important questions about whether endometriosis is one disease or whether different subtypes with different underlying causes exist.

The exome-sequencing study on samples from deep infiltrating endometriosis lesions reported by Anglesio and colleagues in this issue of the *Journal*[5] provides interesting results and shows further complexity of the disorder. They identified somatic mutations in lesions from 19 of 24 patients (79%). The number of mutations in each lesion was variable. Lesions from 5 patients (21%) harbored known somatic cancer driver mutations in *ARID1A*, *PIK3CA*, *KRAS*, and *PPP2R1A*. More detailed experiments on samples from 3 other patients revealed *KRAS* mutations in 2 of them. One patient had two different activating *KRAS* mutations, and the other patient had the same somatic *KRAS* mutation in three separate lesions. Lesions contain multiple cell types, and *KRAS* mutations were detected only in the epithelium and not in the stroma.

Cancer-associated somatic mutations in deep infiltrating endometriosis suggest that they may contribute to the development of some deep infiltrating lesions. The observation of the same