Predicting which coronary angiographic lesion is most likely ultimately to cause a myocardial infarction (MI) remains a challenge. For many years, some have argued that mild coronary lesions (<50% diameter stenosis) are responsible for the majority of MIs. This belief helped to propel the vulnerable plaque revolution, whereby a multitude of invasive techniques were extensively studied in hopes of finding a method for detecting which mild stenosis was going to rupture and result in MI. However, data continue to emerge that suggest more severe, and likely ischemia-producing lesions, are the most “vulnerable” lesion subset and are more likely to cause a subsequent myocardial infarction.

A number of small retrospective studies evaluating patients with prior coronary angiograms suggested that mild coronary stenoses were responsible for most MIs. For example, Little and colleagues evaluated the coronary angiograms performed within 1 month of an MI in 29 patients who had a previous coronary angiogram performed days to more than 6 years prior to the MI. In two thirds of the cases, the most severe stenosis in the culprit artery on the baseline angiogram was <50%, and in all but one, it was <70%. However, this study and others were limited not only by their retrospective nature and small size, but also by the variable follow-up between the baseline angiogram and the MI, which in some cases was as long as 11 years. Moreover, these data were at odds with results from an analysis by Alderman and colleagues comparing baseline stenosis severity with occlusion rates at 5-year follow-up angiography in patients in the Coronary Artery Surgery Study. Of the 430 nonbypassed segments with lesions between 5 and 49%, there was a 2% occlusion rate at 5 years compared with a 24% rate in the 89 segments with lesions between 81 and 95% narrowed.

More recently, investigators have attempted to determine the underlying lesion severity in patients with ST segment elevation MI by analyzing the stenosis severity after either fibrinolysis or aspiration thrombectomy at the time of primary percutaneous coronary intervention. These investigators found that the vast majority of underlying lesions were greater than 50% narrowed. Of course, these findings are limited by the likely presence of residual thrombus and vasospasm.

There are also important data from the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study, which included 700 patients with acute coronary syndromes who underwent percutaneous coronary intervention and 3-vessel intravascular ultrasound examination at the time of their acute coronary syndrome presentation, and then were followed longitudinally for a median of 3.4 years. There was little angiographic disease in the nonculprit vessels at baseline. The lesions responsible for follow-up events in the nonculprit vessels had an angiographic mean diameter stenosis of 32% at baseline, which may explain why the vast majority of events were progression of angina; there were only 6 patients (<1%) with an MI related to a nonculprit vessel during follow-up. At the time of the follow-up angiogram in these patients with nonculprit vessel events, the angiographic disease had progressed to a mean diameter stenosis of 65%.

Two of the baseline intravascular ultrasound parameters most strongly associated with nonculprit lesion adverse events during follow-up were plaque burden and minimum lumen area, both correlates of angiographic lesion severity. No major adverse event occurred in a lesion with a less than 40% cross sectional narrowing at the time of the baseline intravascular ultrasound examination.

These more recent data support the paradigm that plaque rupture with variable degrees of thrombosis and healing is an ongoing process occurring in multiple locations in the coronary arterial system at any given time. When plaque rupture and thrombosis occur at the site of a severe stenosis, it is more likely to result in myocardial ischemia or infarction, as compared with a mild stenosis. Rarely, plaque rupture at the site of a mild stenosis will result in a cardiac event. However, because there are many more mild stenoses, as compared with severe ones, it is not unusual for a patient without known coronary disease or angina to suffer a myocardial infarction.

In this issue of Circulation: Cardiovascular Interventions, a study from Mancini and the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) investigators adds further support to this paradigm. The COURAGE trial randomized 2287 patients with stable coronary disease to either optimal medical therapy alone or to percutaneous coronary intervention and optimal medical therapy. In the current report, the COURAGE investigators identified 489 patients who had clinically driven follow-up
coronary angiograms. The goal of their study was to identify the lesion most likely responsible for the symptoms prompting the follow-up angiogram and to determine its severity at the time of enrollment into the study. In short, they found that the majority of patients who had an MI or acute coronary syndrome requiring percutaneous coronary intervention at follow-up had an originally deferred lesion that was $>50\%$ narrowed. On the follow-up angiogram, the average severity of the lesion responsible for the MI or acute coronary syndrome was $>70\%$ narrowed. The only independent predictors of MI or acute coronary syndrome were male gender and the number of lesions originally $>50\%$ narrowed that had not been revascularized.

The average time between the baseline angiogram and the follow-up angiogram in these 489 patients was 1.3 years, with a median of 0.7 years. Of note, if the baseline severity of the lesion responsible for symptoms at follow-up was $>50\%$ narrowed, then the median follow-up time was 0.59 years, whereas if it was $<50\%$ narrowed, then the median follow-up was significantly longer at 1.22 years, supporting the idea that the milder lesions required more time to progress before causing an event.

It is also important to note that the lesions which were $<50\%$ narrowed at baseline and ultimately were responsible for symptoms and follow-up coronary angiography represented $<4\%$ of all lesions that were $<50\%$ at the time of the baseline angiogram. Lesions which were $>50\%$ narrowed at the time of the baseline angiogram and which ultimately resulted in an MI or acute coronary syndrome represented 21% of all lesions narrowed $>50\%$ at the time of the baseline angiogram. These findings highlight the probability that one will not be able to detect mild lesions that will cause future events, and the need to distinguish which severe lesions are most likely to cause future events.

This study has a number of strengths, including the relatively large number of patients with serial coronary angiograms, the reasonably short time interval between the baseline angiogram and the subsequent event and follow-up coronary angiogram, and the detailed angiographic analysis. Unfortunately, the investigators did not analyze the group of 67 patients who suffered a subsequent MI separately from the 63 patients who underwent angiography because of unstable angina. More specific information about lesion severity at baseline in only the patients who subsequently had an MI, and in particular, those who had an ST segment elevation MI, would have strengthened the study.

Another limitation of the study is the lack of invasive physiological assessment of stenosis severity with fractional flow reserve (FFR) measurement. FFR is now the reference standard for identifying ischemia-producing lesions. The Fractional flow reserve versus Angiography for Multivessel Evaluation (FAME) trial demonstrated that an FFR-guided percutaneous coronary intervention strategy, in which those lesions with an ischemic FFR are stented and those with a nonischemic FFR are treated medically, results in a significant reduction in major adverse events when compared with the standard angiography-guided strategy in patients with multivessel coronary artery disease. Importantly, at 2-year follow-up, there was a $<1\%$ MI rate related to angiographically significant, but hemodynamically insignificant, narrowings (based on a nonischemic FFR), which did not undergo stenting. More recent data demonstrate that patients with proximal left anterior descending lesions that are angiographically narrowed between 30 and 70%, but are not hemodynamically significant by FFR evaluation, have a $<1\%$ MI rate at 5 years and overall survival free of death and MI, which is similar to a matched control population without known coronary artery disease.

Thus, the addition of FFR in the current study would have allowed better discrimination of the lesions which were $>50\%$ into those that were ischemia-producing and those that were not. We have robust data confirming the safety and low event rate of medically treated stenoses that do not have an abnormal FFR. We also have robust data, including data from a previous substudy from the COURAGE trial, documenting the high risk of ischemia-producing coronary disease when identified noninvasively. We have less robust, but suggestive data, implying that lesions with an abnormal FFR are indeed more “vulnerable” and likely to cause a subsequent cardiac event. Two studies showed significantly worse outcomes in patients with coronary lesions with an ischemic FFR who were treated medically, compared with patients with similar nonischemic lesions who also were treated medically.

The ongoing FAME 2 trial should provide more definitive data regarding this hypothesis. In this study, patients with stable angina and coronary disease are undergoing FFR measurement. If at least 1 lesion has an ischemic FFR, then the patient is randomized to FFR-guided percutaneous coronary intervention or to optimal medical therapy. If no lesion has an ischemic FFR, then the patient will be followed in a registry. This design will allow comparison of the MI rate in medically treated patients with stable coronary disease and either the presence or absence of significant ischemia based on FFR.

Why an ischemia-producing coronary lesion with an abnormal FFR would be more likely to cause a subsequent MI when compared with a nonischemia-producing lesion with a similar angiographic appearance remains unclear. Part of the answer may be related to the limitations of the coronary angiogram and the likelihood that ischemia-producing lesions are more severely narrowed than nonischemia-producing ones, despite the similar angiographic appearance. But it also may be that there is increased plaque vulnerability as a consequence of hemodynamic perturbations and altered shear stress occurring in the setting of an abnormal FFR. An intriguing study found a significant relationship between inflammatory cytokine activity and FFR in patients with stable coronary disease.

Based on more recent data, including the study in this issue of Circulation: Cardiovascular Interventions by Mancini and colleagues, we can conclude that an MI is not more likely to result from a mild coronary lesion as compared with a moderate or severe one. Further differentiation of moderate to severe lesions into those that are responsible for myocardial ischemia identifies those lesions at highest risk for causing a subsequent cardiac event. The exact mechanism by which this occurs requires further study.
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References

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