Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 25, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2009.12.070

EDITORIAL COMMENT

Fractional Flow Reserve-Guided Stent Therapy for Multivessel Disease

Taking a Closer Look*

Robert J. Applegate, MD

Winston-Salem, North Carolina

We are entering an era of percutaneous coronary artery stenting with unprecedented deliverability, efficacy, and safety of these devices due in large part to improvements in second-generation drug-eluting stents. Although the early and late outcomes of coronary stent procedures have been extensively evaluated in the past several years, attention has focused recently on the selection of patients who would benefit most from this form of revascularization. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study indicated that revascularization could be safely deferred in patients with chronic stable angina on an optimal medical regimen (1). Appropriateness criteria have been published that outline the clinical situations and lesion types in which percutaneous coronary intervention would be optimal for patients with symptomatic coronary artery disease (CAD) (2). Finally, the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study indicated that fractional flow reserve (FFR) guidance of coronary artery stenting in patients with multivessel CAD resulted in a lower rate of adverse events at 1 year than traditional angiography-guided coronary artery stenting (3).

See page 2816

The FAME study has created tremendous buzz and interest within the cardiology community, particularly among interventionalists. This should not be surprising because the results challenge the long-held belief that the "dye don't lie" (i.e., that optimal stent outcomes are based on angiographic assessment of lesion morphology and severity). Discussions of how the FAME study should change current practice have been numerous, occurring at every level of practice from societies down to individual practitioners. The context in which the FAME study will be interpreted, however, will likely emerge from discussions held on the local level. Important considerations in these discussions will be answers to questions concerning the reproducibility and generalizability of the FAME study results. Will the results be confirmed by other studies? Can we use the FAME study to identify angiographic and FFR subsets that might particularly benefit from FFR-guided stent therapy?

Whether the FAME results will be reproduced in other studies remains to be determined. This is an important issue because of the potential implications of transitioning from angiography-guided to FFR-guided stent therapy. The FFR has been validated as a metric of ischemia in comparison studies with noninvasive methodologies of ischemia detection. Moreover, the prognostic value of an abnormal FFR (i.e., <0.75 to 0.80) has also been evaluated. The DEFER (Deferral of Percutaneous Coronary Intervention) and other small studies using the FFR to guide decision making have indicated that stenting of a lesion with an FFR >0.75 to 0.80 can safely be deferred for up to 5 years (4). What is unique about the FAME study is that the results suggest for the first time that stenting of lesions with an FFR >0.80 in the current era may actually be detrimental. The rationale for this apparent paradox is that although adverse drug-eluting stent–related events occur uncommonly, they are more frequent than the rate of events of a lesion managed by optimal medical therapy alone. In addition to simply confirming the FAME study results, a better understanding of an FFR cutoff (e.g., <0.75 vs. 0.80), assessing the FFR value in patients with acute coronary syndromes, and an economic assessment of widespread FFR use would substantially strengthen a transition to greater utilization of FFR.

With respect to identifying subsets of patients who might benefit most from FFR-guided stent therapy, Tonino et al. (5) in this issue of the *Journal* provide an in-depth evaluation of the relationship between angiographic severity and the FFR in the FFR arm of the FAME study. In the FFR group, 44.1% had lesions of 50% to 70% angiographic severity, 37.5% had lesions of 71% to 90% angiographic severity, 14.3% had lesions of 91% to 99% angiographic severity, and 10.6% had lesions that were totally occluded (p = NS vs. the distribution of angiographic lesion severity in the angiography-guided arm of the study). In those with angiographic 3-vessel disease (approximately one-fourth of the FFR-guided group), only 14% had concordant 3-vessel functional disease (i.e., FFR <0.80 of all 3 vessels), 43% had functional 2-vessel disease, 34% had functional 1-vessel disease, and 9% had no lesions with an FFR <0.80. Interestingly, in those with angiographic 2-vessel disease, the proportion with functional 2-vessel disease was 43%, whereas 45% had functional 1-vessel disease and 12% had no lesions with an FFR

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Section of Cardiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina. Dr. Applegate has received an honorarium from and is on the advisory board of Abbott Vascular.

<0.80. Looked at another way, in the overall FFR arm of the study, the subgroup with angiographic lesion severity of 50% to 70% had an FFR <0.80 in only 35%, which increased to 80% in the group with angiographic lesion severity of 71% to 90% and to 96% in the group with angiographic severity of 91% to 99%.

Although one could raise concerns about the fact that only those in the FFR arm of the FAME study were evaluated in this substudy, important observations can still be made about the study findings. The poor correlation of angiographic and functional measures of lesion severity observed in the FAME study might seem disconcerting at first glance, but should not be surprising. A large portion of the apparent discrepancy between angiography- and FFR-determined severity can be attributed to the well-recognized high interobserver variability in evaluating the severity of coronary stenoses angiographically alone (6). That the greatest degree of discordance between FFR and angiographic lesion assessment occurred in the subgroup with the least extent of angiographic stenosis (i.e., 50% to 70%) is also not unexpected because this range of angiographic severity is associated with the highest degree of interobserver variability in angiographic assessment of stenosis severity. Fortunately, the proportion with an FFR <0.80 in the FAME study increased dramatically in lesions deemed to have angiographic severity >71%, albeit 20% of these lesions still were associated with an FFR >0.80.

Considering the results of this FAME substudy in the context of clinical practice, lesions with intermediate angiographic severity of 50% to 70% appear to represent a diverse mix with respect to ischemia potential, and stenting based solely on an "oculostenotic" basis may not lead to optimal outcomes. The extent to which interventionalists currently perform stenting of lesions with an angiographic severity of 50% to 70% will likely influence the extent to which their practice could be altered by shifting to an FFR-guided strategy. At present, a noninvasive ischemia evaluation is often available before catheterization and can help guide decision making. However, the usefulness of noninvasive testing in multivessel disease is problematic and may not accurately identify all significant lesions accurately (7). If one accepts that the FFR will often be >0.80 and that stenting a lesion with an FFR >0.80 may be detrimental, then it would seem important to assess the FFR in intermediate lesions (i.e., 50% to 70% angiographic severity) before stenting. In those lesions with angiographic severity of 71% to 90%, however, routine use of the FFR will likely be controversial. Because a great majority of lesions with this degree of angiographic severity have an FFR <0.80, routine FFR use to avoid stenting in the 20% who may have an FFR <0.80 may not be clinically or economically reasonable. Ultimately, further studies will need to be performed in those with 71% to 90% angiographic severity to confirm the outcomes of this FAME substudy and strengthen the rationale for use of the FFR in this important patient subset.

It is also important to place the results of the primary FAME study, and this substudy, in the context of the body of knowledge that exists concerning outcomes in patients with multivessel CAD. Historical evaluations of clinical outcomes in patients with symptomatic CAD have traditionally been based on the extent of disease determined angiographically. Although those with 3-vessel CAD are generally believed to have worse long-term outcomes than those with 1- or 2-vessel disease, this clinical impression has not been consistently supported in clinical trials. For example, in the medical arms of coronary artery bypass trials, there were no discernible differences in clinical outcomes among those with 1-, 2-, or 3-vessel CAD treated medically unless there was concomitant left ventricular dysfunction. The basis for this apparent paradox is not well understood. However, the observations from this FAME substudy suggest that the extent of functional multivessel disease cannot be extrapolated from angiography alone, and thus stratification of outcomes based solely on angiographic determination of severity may be clinically flawed. What is missing from this substudy of the FAME study is information about the association between the extent of angiography- and FFR-determined lesion severity and clinical outcomes at 1 year. This type of assessment would provide important support of the overall FAME study results indicating that stent therapy is optimally guided by determination of ischemic potential of a lesion and not by simple angiographic assessment of stenosis severity. Moreover, it would help identify important subgroups that would benefit most from FFR-guided stent therapy.

Finally, it is important to fully understand how patients were selected for inclusion in the FAME study and whether those results can be generalized to all patients with multivessel disease being considered for percutaneous coronary intervention. The results of the COURAGE study (1) and the FAME study (3), suggesting that revascularization can be deferred safely, are at odds with the body of literature indicating that an early invasive strategy with aggressive stenting is superior to medical therapy in patients with an acute coronary syndrome (8). How do we reconcile the apparently divergent results in these 2 groups of patients with symptomatic CAD? The most likely explanation is that the 2 strategies evaluated patients with different and distinct manifestations of CAD: ischemia from flow obstruction resulting in chronic angina and plaque rupture resulting in acute coronary syndromes (9). Patients with these different manifestations of CAD (chronic ischemia vs. acute coronary syndrome) have vastly different short-term adverse event rates, which should not be construed as comparing "apples to apples." Ultimately, further studies examining functional assessment of lesions in patients with unstable angina and non–ST-segment myocardial infarction are needed to define the role of FFR-guided stenting in patients with these clinical syndromes, and it cannot be advocated for use in this clinical situation at this time. Nonetheless, the FAME study, including this more detailed

JACC Vol. 55, No. 25, 2010
June 22, 2010:2822–4

analysis, provides a strong foundation for moving toward ischemia-directed stent therapy in patients with symptomatic CAD.

Reprint requests and correspondence: Dr. Robert J. Applegate, Section of Cardiology, Wake Forest University School of Medicine, 1 Medical Center Boulevard, Winston-Salem, North Carolina 27157-1045. E-mail: bapplega@wfubmc.edu.

REFERENCES

1. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.
2. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization. J Am Coll Cardiol 2009;53:530–53.
3. Tonino PA, de Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
4. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up the DEFER study. J Am Coll Cardiol 2007;49:2105–11.
5. Tonino PAL, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study: Fractional Flow Reserve Versus Angiography for Multivessel Evaluation. J Am Coll Cardiol 2010;55:2816–21.
6. Zir LM, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. Circulation 1976;53:627–32.
7. Lima RS, Watson DD, Goode AR, et al. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of sever three-vessel coronary artery disease. J Am Coll Cardiol 2003;42:64–70.
8. Mehta SR, Cannon CP, Fox KA, et al. Routine vs. selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. JAMA 2005;293:2906–17.
9. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:310–8.

Key Words: coronary angiography ■ drug-eluting stent ■ fractional flow reserve ■ multivessel coronary artery disease ■ percutaneous coronary intervention.