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Thinking Outside the Lumen

Fractional Flow Reserve Versus Intravascular Imaging for Major Adverse Cardiac Event Prediction

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If you always do what you always did, you will always get what you always got

—Albert Einstein (1)

Four decades ago, we believed in a dogma that acute myocardial infarction (MI) resulted from near total luminal obstruction by progressive thickening of coronary atheroma. At that time, pathologists used to report cross-sectional area (CSA) stenosis for the quantification of disease, and thrombosis was considered the consequence and not the cause of MI (2). Only after the description of plaque remodeling (3), did it become clear that quantification by CSA overestimated disease when compared with angiography; for instance, a 75% CSA stenosis was only a 50% (diameter) stenosis in a coronary angiogram. Expanding the concept further, the study of Ambrose et al. (4) demonstrated that progression of coronary artery disease (CAD) to MI occurred predominantly in nonobstructive lesions. Narula et al. (5) have recently explained that the majority of the fateful lesions may substantially enlarge over time before plaque rupture, as previously observed in aortic plaques (6), reconciling the discrepancy between the reports of preceding nonobstructive lesions and significant luminal stenosis at the time of the acute event. Intravascular imaging studies have indeed demonstrated that the lesions likely to result in a major adverse coronary event (MACE) have modest luminal stenosis, large plaque burden, and thin fibrous caps, but evolve voluminously to result in significant stenosis at the time of the acute event (7). It has become increasingly clear that regardless of the initial luminal stenosis, the evolving plaque burden and attenuated fibrous cap comprise the major determinants of plaque rupture in patients with acute coronary syndromes (ACS) (5–7); most plaques at the time of rupture are huge and significantly obstructive. On the other hand, significantly obstructive, but predominantly fibrotic, lesions may be associated with angina and the need for revascularization. As such, fibrotic lesions not result in ACS. Therefore, increasing plaque burden and luminal stenosis predispose to both ACS as well as angina requiring revascularization. As such, the main determinant of atherothrombosis progression is plaque composition. Hence, plaque characterization should enhance risk stratification beyond coronary angiography or physiological testing. It is therefore prudent to ask whether fractional flow reserve (FFR) with intravascular imaging would be superior to FFR alone?

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Lessons From Patients With Chronic Stable Angina: Courage, FAME II, and the Role of FFR

Multiple randomized trials in patients with chronic stable angina comparing percutaneous coronary intervention (PCI) versus surgical revascularization established a 5-year event rate of 16.9% and 16.7%, respectively (8). The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial documented no difference between optimal medical therapy (OMT) and OMT + PCI at higher event rates of 20% and 19.5%, respectively (9), and proposed a powerful concept, that is, not every lesion obstructive by angiography needs to be revascularized.

It became clear that symptomatic patients with multivessel CAD needed better risk stratification, and FFR was tested prospectively in the FAME (Fractional Flow Reserve Versus Angiography for Guiding PCI in Patients With Multivessel Coronary Artery Disease) trial (10). The study identified that 37% of lesions morphologically obstructive by angiography were FFR negative. Avoiding PCI in these (less critically stenotic) lesions resulted in a 5% absolute reduction in death, nonfatal MI, and repeat revascularization at 1 year (10). Therefore, exclusion of FFR-negative lesions allowed for selection of the subset of patients who might truly benefit from PCI. In the logical extension of this strategy, the randomized FAME II trial compared OMT and OMT + PCI in the FFR-positive lesions. OMT + PCI emerged superior when compared with OMT alone in FFR-positive lesions. However, the events were primarily driven by urgent revascularization (1.6% vs. 11.1%; $p < 0.0001$) without a difference in death or MI (11). The number needed

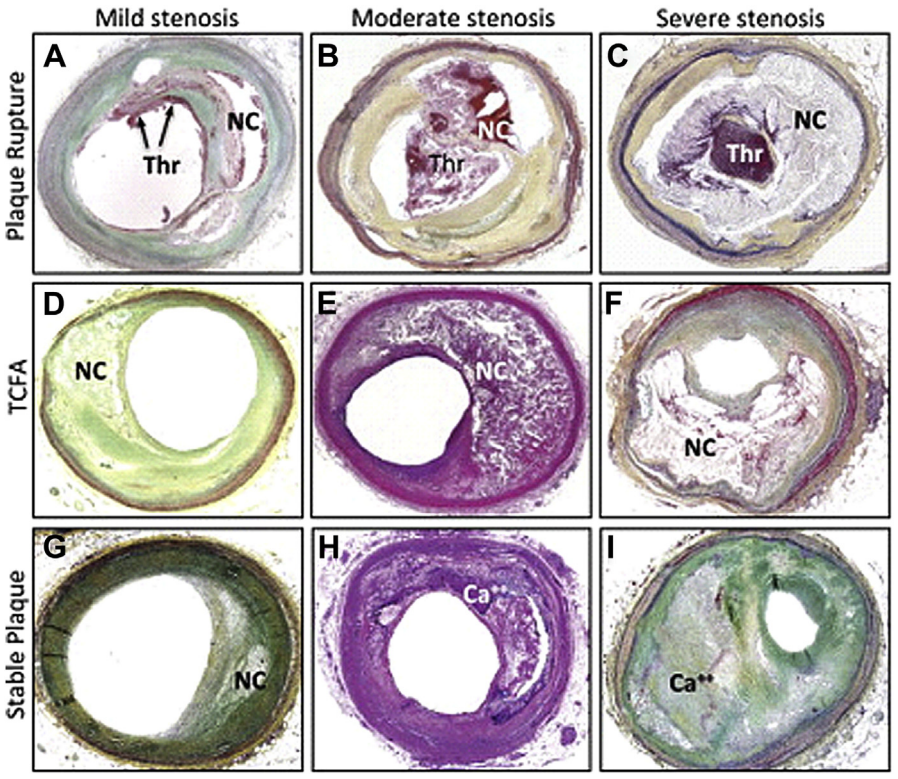

Figure 1 Why Imaging Can Risk Stratify CAD Beyond Angiography and FFR

This figure illustrates 3 different risk levels for coronary atherosclerosis at 3 different levels of stenosis. **(Upper row)** Highest risk **(A to C)**: ruptured plaques. Please notice that lipid-rich plaques can precipitate fatal coronary thrombosis at different degrees of stenosis, including: mild **(A)**, moderate **(B)**, and severe **(C)**. However, all 3 lethal plaques share the same composition, that is, lipid-rich, thin fibrous cap. Coronary angiography and fractional flow reserve (FFR) can only identify the severely stenotic plaque, and therefore miss the mildly and moderately obstructive. However, intravascular imaging will identify all 3. **(Middle row)** Intermediate risk **(D to F)**: thin-cap fibroatheromas. As illustrated in thrombotic plaques, only intravascular imaging will correctly identify all 3 plaques as high risk, independent from the degree of stenosis. **(Lower row)** Lowest risk **(G to I)**: fibrotic plaques. Again, all 3 stable plaques can be properly identified by imaging. However, coronary angiography and FFR will identify the severely stenotic plaque **(I)**. Furthermore, this lesion will be classified as high risk. However, severely stenotic, fibrotic plaques may be just a marker for advanced disease but will not evolve with plaque rupture and thrombosis. (See text for details). CAD = coronary artery disease; NC = necrotic core; TCFA = thin-cap fibroatheroma; Thr = thrombus. Adapted with permission from Narula et al. (5).

to treat affirmed that 10.5 FFR-positive lesions must undergo intervention to prevent 1 episode of revascularization.

Lessons From Patients With ACS: PROSPECT, VIVA, PREDICT, and the Role of Intracoronary Imaging

ACS patients are at risk of recurrent coronary events from the progression of nonculprit lesions (NCL). Contrary to the COURAGE and FAME II trials in patients with stable angina, studies in ACS successfully treated all culprit and angiographically obstructive lesions before evaluating NCL by intravascular imaging. Hence, the role of obstructive disease in triggering future events was eliminated from the beginning. In the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study (7), the average percent diameter stenosis for NCL responsible for future coronary events (the high-risk plaque) at 3.4 years was 32 ± 21%; almost all NCL triggering future coronary events were <70% diameter stenosis, similar to the original proposal of the Ambrose-Fuster study (4). However, at the time of the subsequent event, these NCL had expanded to 65 ± 16% luminal diameter stenosis. Therefore, a high-risk plaque can precipitate plaque rupture and thrombosis at a wide range of angiographic stenoses, from mild to severe, as documented in the PROSPECT trial, and illustrated in Figure 1.

When analyzing morphological features, plaque burden emerged as the strongest independent predictor for clinical events (hazard ratio 5), along with virtual histology intravascular ultrasound–verified thin-cap fibroatheroma, and a minimal luminal area ≤ 4 mm^2 (7). Simultaneous presence of these 3 parameters was associated with an 18% incidence of future MACE at 3.4 years (hazard ratio: 11.5) (7). Such high-risk plaques were rare, present in only 4.2% of all plaques studied (12). Although most plaques were not critically occlusive to start with, they expanded substantially in the interim, and evolved to demonstrate large cross-

sectional area stenosis, as previously seen in pathology studies, confirming the plaque expansion hypothesis of Narula et al. (5). Two additional imaging studies, the VIVA (VH-IVUS in Vulnerable Atherosclerosis) and the PREDICTION (Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology) trials also identified plaque burden >70% as a powerful independent predictor (13,14). Finally, the Motoyama et al. (15) study identified low attenuated and positively remodeled, large, nonobstructive plaques by computed tomographic angiography to be associated with a 22.5% risk of developing ACS after 2 years. As reported in the PROSPECT trial, the incidence of these high-risk plaques was only 4.5%. Most importantly, low attenuated plaques were amenable to reductions in plaque volume after statin therapy (16).

Integrating FFR With Intravascular Imaging for the Prediction of Events

Before the FAME II study, obstructive lesions by angiography could be treated by OMT with or without revascularization. After FAME II, functional evaluation of these lesions has become the unwritten standard of management. If the lesion is FFR-negative, OMT may be the best option, and PCI may not improve an event-free survival. However, if the lesion is FFR-positive, PCI is indicated, and is expected to obviate the need for urgent revascularization.

What may happen if an FFR-positive lesion is left for OMT alone? The FAME II–based penalty may be the need for urgent revascularization in the short term. However, the data are evolving that the obstructive lesions may eventually lead to death and MI (17). On the other hand, not necessary all FFR-positive lesions will benefit from revascularization. As stated earlier, <15% of FFR-positive lesions lead to cardiovascular (CV) events. OMT alone can reduce ischemic burden and improve prognosis (18), and FFR-positive lesions may still be suitable for regression. This was the rationale for the recently reported YELLOW (Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy) trial (19), which randomized patients with multivessel CAD and stable angina to high-dose rosuvastatin 40 mg versus standard of care statin therapy. After successful PCI of culprit lesions, the remaining obstructive, FFR-positive, NCL was evaluated by near infrared spectroscopy and intravascular ultrasound. The primary objective was reduction in lipid content. The study was not powered for clinical events. After 7 weeks of therapy, lesions randomized to the intensive group showed a significant reduction in lipid content. Of potential clinical value, large regression in lipid plaques also showed a trend towards improvement in FFR (19). The YELLOW trial provided evidence that aggressive statin therapy can induce regression in lipid-rich plaques, even when FFR-positive and severely obstructive by angiography. Importantly, no change was observed in the lipid content (and FFR) by either therapy if the plaque was fibrous to begin with. These plaques may not harbor an increased risk of plaque rupture and thrombosis. Therefore, it is conceivable that risk stratification would improve over and above quantitative assessment by using qualitative assessment of the plaque outside the lumen. Optimal imaging quality obtained by optical coherence tomography studies demonstrate the ability to detect multiple, complex coronary plaques in high-risk patients, and may evolve to be the gold standard for quantification of the fibrous cap in vivo. However, despite the image quality, outcome research in OCT is scarce and needs to fulfill these expectations (20). High-dose statins and further improvements in medical therapy, including PCSK9 antibodies, harbor great potential to further reduce future events (21). For high-risk plaques, significant reductions in lipid may potentially be the first step for improvements in flow (19). Conversely, lack of regression may reflect impending progression to clinical events. Similarly, fibrotic lesions may be properly treated by OMT, and are least likely to result in ACS. However, if clinically refractory to OMT, PCI could be offered at a later date.

Although FFR is a useful tool to guide clinicians in clinical practice, is it safe to leave all FFR-negative, but angiographically severe, lesions without revascularization? Not really. At least 3% of FFR-negative lesions in the FAME study resulted in MACE at 2 years. Most importantly, the benefit of FFR-guided PCI lost statistical significance when compared with angiographic-guided PCI at 2 years ($p = 0.08$) (22). For nonobstructive disease, the PROSPECT study demonstrated that despite the OMT, 11.6% of lesions developed MACE. Because they were less stenotic, a longer period was needed to develop adverse events. Plaque composition played a major role, with only 0.7% MACE at 3 years for fibrotic lesions compared with 2.7% for lipid-rich fibroatheromas ($p < 0.0001$) (23). The Motoyama et al. (15) study of CT angiography demonstrated that the larger the plaque burden and greater the necrotic core, the earlier and higher the likelihood of an adverse event. The evidence is clear that FFR will identify lesions at risk to develop MACE earlier. However, loss of statistical power after 2 years suggests that longer follow-up may show angiography-driven and FFR-driven curves converging with similar event rates.

The field of high-risk atheroma and prevention of MACE is evolving rapidly. After consideration of the aforementioned trials, 2 important issues remain disturbing, and deserve future investigation. First, the evolution of NCL to an eventful state is not clear. Second, the MACE that occur in asymptomatic subjects before reaching any medical attention are not beneficiary of the research directed at the imaging or hemodynamic significance.

Conclusions

Current analyses in patients with presumably stable angina suggest that FFR-guided PCI will reduce short-term

revascularization, but not major CV events. However, in the long term, some of these lesions may develop major events, including death and MI. Although FFR was an improvement over angiography, only a few of the FFR-positive, obstructive lesions were associated with CV events. In this group, FFR could not separate between high-risk and relatively benign lesions. Intravascular imaging can see beyond luminal obstruction, and may represent the next frontier to risk stratify these patients. At the same time, contemporary analyses in patients with ACS demonstrate that most recurrent events arise from positively remodeled plaques with a large atherosclerotic burden, which may not necessarily be obstructive by angiography at that time. FFR has little role in the setting of nonobstructive disease, and may even misclassify these lesions. Imaging may be the only way to detect and characterize high-risk, nonobstructive disease. Current and promising aggressive medical therapies could help avoid expansion of such lipid-rich plaques, and the refractory lesions may be deserving of revascularization.

Angiographic, physiological, and imaging data are complementary and synergistic in the search for preventing future MACE. Elucidating the expansive process preceding ACS may be fundamental to get there. However, from nonobstructive to thrombotic plaques, the lumen itself is predominately an innocent bystander. Thinking out of the lumen is fundamental, now more than ever.

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REFERENCES

1. Food4Innovations: Food, Innovation and Technology. Available at: http://wouterdeheij.wordpress.com/2013/04/27/famous-innovation-quotes-from-steve-jobs-gunter-pauli-einstein-henry-ford-and-many-others/. Accessed February 27, 2014.
2. Roberts WC, Buja LM. The frequency and significance of coronary arterial thrombi and other observations in fatal acute myocardial infarction: a study of 107 necropsy patients. Am J Med 1972;52:425–43.
3. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5.
4. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56–62.
5. Narula J, Nakano M, Virmani R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. J Am Coll Cardiol 2013;61:1041–51.
6. Moreno PR, Purushothaman KR, Fuster V, O'Connor WN. Intimomedial interface damage and adventitial inflammation is increased beneath disrupted atherosclerosis in the aorta: implications for plaque vulnerability. Circulation 2002;105:2504–11.
7. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.
8. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146–54.
9. 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.
10. 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.
11. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.
12. Moreno PR. The high-risk thin-cap fibroatheroma: a new kid in the block. Circ Cardiovasc Interv 2009;2:500–2.
13. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) study. J Am Coll Cardiol Img 2011;4:894–901.
14. Stone PH, Saito S, Takahashi S, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION study. Circulation 2012;126:172–81.
15. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009;54:49–57.
16. Inoue K, Motoyama S, Sarai M, et al. Serial coronary CT angiography-verified changes in plaque characteristics as an end point: evaluation of effect of statin intervention. J Am Coll Cardiol Img 2010;3:691–8.
17. Mancini GB, Hartigan PM, Bates ER, et al. Angiographic disease progression and residual risk of cardiovascular events while on optimal medical therapy: observations from the COURAGE trial. Circ Cardiovasc Interv 2011;4:545–52.
18. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283–91.
19. Kini AS, Baber U, Kovacic JC, et al. Changes in plaque lipid content after short-term, intensive versus standard statin therapy: the YELLOW trial (Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy). J Am Coll Cardiol 2013;62:21–9.
20. Finn AV, Chandrashekhar Y, Narula J. IVUS and OCT: either or survivor. J Am Coll Cardiol Img 2011;4:1047–9.
21. Vogel RA. PCSK9 inhibition: the next statin? J Am Coll Cardiol 2012;59:2354–5.
22. Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 2010;56:177–84.
23. Dohi T, Mintz GS, McPherson JA, et al. Non-fibroatheroma lesion phenotype and long-term clinical outcomes: a substudy analysis from the PROSPECT study. J Am Coll Cardiol Img 2013;6:908–16.

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