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EDITORIAL COMMENT

FFR_{CT}

Solid PLATFORM or Thin Ice?*

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Since the introduction of coronary angiography in 1958 and the near-simultaneous emergence of exercise stress testing, clinicians have wrestled with the controversy of whether it is better to pursue direct anatomic evaluation of coronary stenosis or physiologic evaluation of ischemia in patients with stable ischemic heart disease (SIHD) (1). Whereas classical observational studies have concluded that noninvasive ischemia testing helps to stratify risks and benefits of medical therapy versus percutaneous coronary intervention (PCI) (2), modern randomized trials have not demonstrated such a benefit to diagnosing ischemia or performing PCI for SIHD (3,4). Thus, today the diagnosis and management of SIHD is in many ways as unclear as ever and perhaps even more confusing due to the myriad of noninvasive testing options, including coronary computed tomography angiography (CCTA).

The clinical appeal of coronary angiography (invasive or noninvasive) is that it provides direct visualization of plaque morphology and degree of stenosis. The problem with this approach is that the percentage of stenosis has poor correlation with coronary blood flow (5) and, consequently, is an inadequate surrogate for physiologic significance (6). Anatomic imaging is also wedded with the "oculostenotic" reflex and often leads to revascularization without an apparent prognostic advantage, thereby increasing the cost of care (7–9). On the other hand, stress imaging for SIHD has imperfect sensitivity and specificity (10), thereby leaving cardiologists with the difficult choice between the sometimes uncertain clinical significance of stress test results versus anatomic imaging for stenosis with the potential instant visual gratification of opening arterial stenosis by PCI.

In 2005, the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial did not demonstrate a clinical benefit to initial PCI versus guideline-directed medical therapy in SIHD. Additionally, a quality-of-life substudy of COURAGE showed a small benefit to PCI that was no longer significant after 36 months (11). More recently, the STICH (Surgical Treatment for Ischemic Heart Failure) trial (12), the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial, and 2 meta-analyses (13,14) have not identified prognostic benefit from a strategy of initial routine revascularization for SIHD. One meta-analysis did report symptom relief after PCI, but no benefit to mortality, myocardial infarction (MI), or repeat PCI (15). Some posit that studies of ischemia-driven patient care and PCI versus medical therapy have enrolled too many low-risk patients and point to the initial results of a COURAGE substudy, which was underpowered but suggested that patients with a large burden of ischemia (>10% of the left ventricular myocardium) tended to garner a reduction in death or MI ($p = 0.001$ unadjusted; $p = 0.08$, risk-adjusted) if achieving a >5% reduction in ischemia (by medical therapy or revascularization). Unfortunately, a subsequent reanalysis of the COURAGE data found no apparent benefit to ischemia reduction by adding revascularization to guideline-directed medical therapy (16). This lack of demonstrated benefit for ischemia testing to guide management in SIHD in COURAGE and other trials led to the formation of the ISCHEMIA (International Study of Comparative

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Health Effectiveness with Medical And Invasive Approaches) in 2012 (3,4).

On the other hand, the FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) trial has demonstrated that a physiologically guided strategy using fractional flow reserve (FFR) before coronary intervention was superior to an angiographically guided approach for reducing a composite endpoint of death, MI, and coronary revascularization at 1 year, while reducing the number of unnecessary PCI and costs (17). However, in spite of interventional cardiologist expert consensus recommendation (18) for the use of FFR to guide revascularization decisions for 50% to 90% coronary stenosis and multivessel disease, use of FFR in the NCDR (National Cardiovascular Data Registry) has been reported as 6.1% of all intermediate lesions that underwent PCI (19). While recognizing the limitations and confusion in the published reports, the most recent American and European guidelines for the management of SIHD recommend demonstration of greater than mild ischemia before consideration of revascularization (20,21).

Can FFR be estimated without coronary catheterization today at a level of accuracy and reliability appropriate for individual patient-level decision making?

The emergence and rapid evolution of CCTA in the 2000s led to facile noninvasive evaluation of coronary stenosis with high sensitivity to exclude significant angiographic coronary artery disease (CAD). The excellent sensitivity of CCTA makes the test ideal for selected low-intermediate-risk patients, but the low specificity of the test has been its Achilles heel (30% to 42% specificity compared with invasive FFR) (22–24). Thus, concern has arisen that intermediate stenoses, once identified by CCTA, may in comparison to alternative diagnostic methods such as stress imaging, lead to increased rates of invasive angiography and coronary revascularization of unproven clinical benefit in SIHD (8,9,25).

In 1822, French engineer Claude-Louis Navier and Irish mathematician George Gabriel Stokes described scientific principles of conservation of mass and momentum as applied to movement of viscous fluids that laid the foundation for computational fluid dynamics with what eventually would come to be recognized as the Navier-Stokes equations. Over 150 years later and with the evolution of modern supercomputers, Dr. Charles Taylor and his colleagues from HeartFlow have reported success with the use of CCTA data acquired at rest (without the use of adenosine-stimulated hyperemic challenge as is performed in the catheterization laboratory) to solve numerous fluid dynamics equations to noninvasively estimate lesion-specific FFR (26). Aside from fractional flow reserve estimated using computed tomography (FFR_{CT}), other methods to conduct a "one-stop shop" evaluation of coronary stenosis include hybrid CCTA-positron emission tomographic imaging (27), CCTA combined with stress perfusion (28), and coronary transluminal attenuation gradients (29). All these methods have the potential to improve the subpar specificity of CCTA, although none has demonstrated superiority to FFR_{CT} and each poses its own unique logistical challenges such as increased radiation, scan time, post-processing work, and cost. Thus, the medical community currently shares a great interest in the promise and potential of FFR_{CT}.

Despite the enthusiasm for FFR_{CT}, however, studies to date have shown only modest results with regard to the incremental value that the FFR_{CT} information adds to CCTA data. First, the DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Non-Invasive Fractional Flow Reserve) study demonstrated that the addition of FFR_{CT} to CCTA did not improve the sensitivity to detect lesions with invasive FFR <0.8 (91% for CCTA alone vs. 88% for CCTA + FFR_{CT}) but did improve the specificity of CCTA alone from 40% to 82% (23). Next, the DEFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic AngiOgraphy) study similarly demonstrated that sensitivity for detection of stenoses with invasive FFR <0.8 remained comparable for CCTA alone versus CCTA + FFR_{CT} (84% vs. 90%), but specificity only marginally improved from 42% to 54%, and the study did not reach its pre-specified primary endpoint for improving specificity. After this, HeartFlow reported improvements to the software algorithm for computation of FFR_{CT} and the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) study showed a sensitivity of 94% versus 86% for CCTA alone versus CCTA + FFR_{CT}, and specificity of 34% versus 79%, respectively (24). The NXT study is an encouraging improvement to CCTA alone, but it demonstrates an accuracy of FFR_{CT} now approaching single-photon emission computed tomography or stress echocardiography although potentially inferior (without direct comparison) to stress magnetic resonance imaging or positron emission tomography (10).

Although randomized controlled trial data have established invasive FFR as the gold standard for guiding revascularization, we cannot accept a mathematical estimate of FFR (FFR_{CT}) at prima facie with equal enthusiasm. Whereas aggregate data show

encouraging trends in accuracy, at the individual patient level, the ability of FFR_{CT} to accurately change stenosis evaluation should be carefully considered due to the lack of precision leading to a wide confidence interval. Thus, from DISCOVER-FLOW (23), a point estimate of $FFR_{CT} = 0.8$ could have a 95% confidence interval (CI) ranging from 1 (non-flow-limiting) to 0.57 (severely flow-limiting) (30). By comparison, for invasive FFR = 0.8, the 95% CI would range from 0.76 to 0.84 (31). Also, FFR_{CT} does not presently incorporate the influence of microvasculature or collateral circulation on coronary flow, and the clinical impact of this limitation is not known. Currently, there are no randomized controlled trial outcomes data of FFR_{CT} that demonstrate an incremental benefit to CCTA alone or other noninvasive testing, although multiple studies are ongoing.

OBSERVATIONAL SUBSTUDY OF COST AND QUALITY OUTCOMES IN THE PLATFORM TRIAL

The PLATFORM (Prospective Longitudinal Trial of FFR_{CT}: Outcomes and Resource Impacts) study was a cohort study designed to test the impact of combined CCTA + FFR_{CT} upon the rate of invasive coronary angiography (ICA) without obstructive stenosis, costs, and clinical outcomes including death, MI, and quality of life (QOL). PLATFORM recruited patients into 1 of 2 strata (noninvasive and invasive) based upon the type of testing that was planned before enrollment in the study. The study showed that the use of CCTA + FFR_{CT} among those with intended referral to ICA resulted in a 61% reduction in unnecessary catheterizations (ICA without obstructive stenosis) (1). Among patients with planned noninvasive screening, the rates of finding no obstructive CAD at ICA were 13% in patients receiving CCTA + FFR_{CT} and 6% in those undergoing usual care (1). In this issue of the *Journal*, Hlatky et al. (32) report observational data regarding economic and QOL implications of testing strategies within PLATFORM. For patients enrolled in the planned noninvasive testing stratum, the associated cost was higher with CCTA + FFR_{CT} than with usual care including stress testing, but QOL improved. However, for patients with planned referral to ICA, the use of CCTA + FFR_{CT} was associated with a 32% reduction in cost but no change in QOL.

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Like all cohort data, these observations do not infer causality, and it is difficult to rectify why QOL was improved in the noninvasive but not invasive subgroup, yet cost showed the opposite result. More importantly, translating these results to clinical practice might prove challenging. First, clinicians will not choose between FFR_{CT} and direct referral to ICA for patient care decisions, especially among low-intermediate-risk patients with stable symptoms, such as those enrolled in PLATFORM. Rather, the clinical choice would be between CCTA + FFR_{CT} and stress testing, which was not used in patients not receiving FFR_{CT}. The use of stress testing would have resulted in a similar reduction in the number of unnecessary ICA, as shown in the planned noninvasive stratum of PLATFORM and in other studies (33,34), and even lower costs than testing with CCTA + FFR_{CT} would. Thus, the clinical utility of the observed lower cost with CCTA + FFR_{CT} versus direct ICA for low-intermediate-risk patients with SIHD is uncertain. Second, the study was not powered to demonstrate an improvement in death or MI, and after unblinded interventions (PCI or intensified medical therapy) with no sham intervention, subjective improvements in self-reported symptom scales cannot be distinguished from placebo effect by the current study design. Furthermore, the study offers some insight as to how changes in medical therapy might improve symptoms (e.g., statins that may reduce ischemia), but the design unfortunately did not call for reporting of adjustment of antianginal therapy. Third, all previous CCTA research has lauded the high negative predictive value of stenosis <50% by CCTA, so clinicians should carefully consider the incremental benefit of using FFR_{CT} versus CCTA alone for nonobstructive lesions. In fact, a large multicenter registry (35), a meta-analysis of CTA cohort studies (36), and also the PROMISE trial (9) demonstrated that most low-intermediate-risk patients referred to CCTA with stable chest pain do not have obstructive CAD. Finally, the recently published SCOT-HEART (CT Coronary Angiography in Patients With Suspected Angina Due to Coronary Heart Disease) trial (34) concluded that most stable CAD patients could be evaluated by CCTA plus exercise stress test, for less cost and without a 1 to 2 day wait time or need to send patient data to an outside center for processing the FFR_{CT}.

WHAT'S NEXT

Certainly, the PLATFORM cost and QOL analysis adds to the published data due to the lack of cost data available and the great interest in the emerging science of anatomically derived physiologic metrics such as FFR_{CT}. The way forward should include randomized trials that evaluate the incremental change

to cost and outcomes comparing FFR_{CT} versus CCTA with or without stress testing, versus stress testing without CCTA. Additionally, it would be useful to understand the ability of FFR_{CT} to successfully evaluate CCTA acquired in routine practice, which may be of lower image quality than that obtained at expert centers in clinical trials. It would also be important to understand the accuracy of FFR_{CT} derived from CCTA scans with aggressive radiation dose-reduction such as 80 kV that have increased image noise. In order to routinely consider FFR_{CT}, clinicians should be confident that sending patient data to a data processing center for a 1 to 2 day wait and additional significant cost has some value beyond what could be accomplished by conventional CCTA or by combining CCTA with functional testing, such as exercise testing or stress imaging.

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