The overarching goal of noninvasive testing in patients with symptoms suggestive of coronary artery disease (CAD) is to assess the risk for future cardiovascular events and guide clinical care. This includes identifying those at highest risk for obstructive CAD and ischemia that would benefit from coronary revascularization, as well as those at lowest risk for whom an invasive CAD evaluation represents an unnecessary risk. Data from the National Cardiovascular Data Registry has revealed that almost 40% of coronary angiograms are normal or near normal.¹ This suggests that more effective strategies are needed to distinguish between patients with and without significant CAD and better guide the use of invasive coronary angiography (ICA). In symptomatic patients with an intermediate probability of disease, the ideal noninvasive test should be capable of both accurately diagnosing and excluding significant CAD. Historically, significant CAD has been synonymous with obstructive CAD (≥70% stenosis), as determined by angiographic appearance during ICA. However, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial revealed that anatomically obstructive lesions do not always equate to functionally significant lesions as assessed by fractional flow reserve (FFR), an index of the physiological significance of a coronary stenosis.² Furthermore, patients revascularized for lesions that were both anatomically and functionally significant had a 28% lower rate of death, nonfatal myocardial infarction, and repeat revascularization than those patients revascularized on the basis of anatomic stenosis alone. Therefore, if revascularization of stenotic coronary lesions that induce ischemia can improve patient outcomes, then the question is: Can this be accurately identified with noninvasive testing so that only patients with clinically significant CAD are sent for invasive evaluation? Currently, noninvasive testing is capable of evaluating either anatomic or functional significance, but not both in a single modality. Test selection requires choosing between an anatomic or functional evaluation. Cardiac computed tomography angiography (CCTA) is capable of noninvasively assessing the anatomic severity of CAD, whereas stress myocardial perfusion imaging (MPI) by single photon computed emission tomography, positron emission tomography, and cardiac magnetic resonance (CMR), or stress wall motion imaging (WMI) with stress echocardiography (stress echo) or CMR, detect myocardial ischemia and indicate the presence of functional CAD.

**See Article by Neglia et al**

In this issue of *Circulation: Cardiovascular Imaging*, Neglia et al³ studied stable chest pain patients to examine which noninvasive imaging technique had the highest diagnostic accuracy for the detection of obstructive CAD, which was largely determined by anatomic ICA findings. All 475 patients included in the final analysis of the Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease (EVINCI) trial underwent anatomic imaging with CCTA and functional imaging with either single photon computed emission tomography, positron emission tomography, stress echo, or CMR. Those with negative noninvasive imaging results were assumed to not have obstructive CAD without further verification. Three hundred and seven patients had ≥1 abnormal noninvasive test and subsequently underwent ICA; obstructive CAD was identified in 140 patients (29%). When compared with ICA, CCTA was more accurate than functional imaging for the detection of obstructive CAD (area under the curve =0.91 versus 0.74 for MPI and 0.70 for WMI; *P*<0.001). This work confirms the diagnostic performances demonstrated in previous studies, that is, high negative predictive value of CCTA, high sensitivity of MPI (single photon computed emission tomography and positron emission tomography), and high specificity of WMI (stress echo and CMR).³⁴ However, these prior studies were either retrospective meta-analyses of diagnostic performance or prospectively compared only 1 or 2 noninvasive modalities to ICA. Thus, this multicenter, prospective study is the first to simultaneously evaluate the diagnostic ability of multiple contemporary imaging modalities in a single population of symptomatic patients without known CAD. Furthermore, EVINCI incorporated both site-based (local) interpretations of the noninvasive imaging modalities, simulating real-world clinical practice, as well as modality-specific core laboratory analyses.

The importance of core laboratory analysis is to provide uniform expert interpretation and to minimize bias that may be present at the clinical sites. For example, core laboratory physicians were blinded to the clinical and imaging data, whereas local interpreting physicians had access to patients’ clinical data, may have known these patients were participating in a trial studying functional versus anatomic CAD evaluation, and most importantly, were not blinded to the results of the other noninvasive testing, which may have influenced the opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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their interpretation. However, in the final analysis of the trial, the core laboratory results were largely disregarded in favor of the significantly more positive site-based results. The differences in overall diagnostic performances were not nearly as great when analyzed by core laboratory results. Furthermore, the trial was limited by a large proportion of dropouts and protocol violations. Of the 697 patients initially enrolled, 78 (11%) dropped out and 144 (21%) were excluded for protocol violations, including (1) not undergoing ICA despite positive noninvasive imaging, (2) failure to have both CCTA and functional stress imaging, or (3) lacking FFR assessment in patients with intermediate coronary stenosis at ICA. By excluding these patients and failing to analyze on an intention to test basis, the results were subject to referral and selection bias that may have influenced the diagnostic performance of the noninvasive modalities. Although some of these flaws are recognized by the authors, whose attempts to adjust for such biases are unusual yet admirable, use of a trial design that did not require such corrections would have been preferable.

Anatomic assessment during ICA was used as the gold standard for determination of obstructive CAD. No visually obstructive lesions (stenosis ≥70%) were assessed for physiological significance with FFR, and in only a minority of intermediate stenosis (30% to 70% stenosis) was FFR performed. The investigators rightly acknowledge that this favors higher diagnostic accuracy for CCTA, in that 2 anatomic techniques are more likely to agree than when a functional modality is compared with an anatomic one. Nonetheless, angiographic stenosis is a flawed gold standard that does not take into account functional significance. We need to acknowledge the shortcomings associated with using angiographic stenosis and use a more adequate surrogate for the detection of significant CAD. Additionally, functional disease at the level of the microvasculature may produce cardiac symptoms that go undetected in evaluations that only use an anatomic evaluation of epicardial coronary arteries, such as CCTA and ICA. In contrast, noninvasive functional testing may be abnormal in these patients, particularly among women in whom the prevalence of microvascular dysfunction is much greater and associated with adverse outcomes. Because microvascular dysfunction typically requires invasive provocative testing to confirm, the failure to perform this in the current study may have erroneously increased the rate of false positives in functional imaging, thus diminishing the diagnostic accuracy of stress MPI and WMI.

Similar to prior work, this study does not examine the prognostic potential of noninvasive imaging, nor how noninvasive imaging influences outcomes in patients with stable CAD. The authors assume that demonstrating superior diagnostic accuracy for the anatomic evaluation of obstructive CAD with CCTA is more beneficial than identifying or excluding functionally significant lesions with stress MPI and WMI. This is an assumption that should be considered carefully, especially in light of the FAME trial, which demonstrated that stable CAD patients revascularized for ischemia-guided lesions had better outcomes than those undergoing stenosis-guided revascularization. If an alternative, more clinically relevant end point for assessing diagnostic accuracy had been used in the EVINCI trial, such as coronary revascularization, which was performed in 54% of patients with a positive CTA and 50% with positive WMI (48% stress echo and 56% CMR), then CCTA and WMI were nearly equivalent in their ability to identify patients requiring revascularization. Although this reference standard is still limited by lack of a physiological assessment with FFR, it more directly reflects patient outcomes. Ultimately, noninvasive testing should guide patient care to optimize clinical outcomes, rather than just identify what predicts the results of another test.

The ability to have both anatomic and functional information in a single noninvasive modality (a one-stop shop) has the potential to more accurately identify or exclude clinically significant CAD than either an anatomic or functional test alone. The recent development of noninvasive FFR by computed tomography (FFR$_{CT}$) used in conjunction with CCTA may make this a reality. This is supported by the Diagnosis of Ischemia-Causing Stenosis Obtained via Noninvasive Fractional Flow Reserve and Analysis of Coronary Blood Flow Using CT Angiography: Next Steps trials, which demonstrated that CCTA with FFR$_{CT}$ had superior diagnostic performance for the detection of ischemia-causing coronary lesions than CCTA alone.10,11 CCTA with FFR$_{CT}$ has the potential to have the highest accuracy for identifying or excluding anatomically and physiologically significant CAD and determining whether there is a need for revascularization, therefore positively influencing patient management, particularly referrals for ICA. Clinical trials are underway to explore the effect of such information on diagnostic decision-making and processes of care (Prospective Longitudinal Trial of FFR$_{CT}$: Outcome and Resource Impacts [PLATFORM trial], https://clinicaltrials.gov/ct2/show/NCT01943903).

In summary, this study by Neglia et al highlights the diagnostic capabilities of noninvasive imaging for identifying anatomically significant CAD at ICA and found that CCTA demonstrated the highest diagnostic accuracy. However, this trial lacked an invasive evaluation of functional/physiological significance, which current guidelines recommend be used to guide revascularization caused by the effect of ischemia-guided revascularization on future outcomes.12 Although use of a better gold standard will provide much needed refinements in determining test performance, in the current era, the question must be asked: is assessing diagnostic accuracy alone sufficient? The test performance of functional and anatomic noninvasive imaging is well established by prior work, and the present study provides confirmatory evidence. However, going forward, we need to increase our focus on the patient in addition to evaluating test performance. The intent of noninvasive testing is to guide patient management and reduce future cardiovascular events, a goal that is not fully realized by just identifying or excluding disease. The prognostic potential of noninvasive imaging and how testing strategies influence the outcomes of patients with chest pain has not been well studied. The Prospective Multicenter Imaging Study for Evaluation of Chest pain study was designed to compare the clinical effectiveness of initial functional testing to a strategy of initial anatomic imaging with CCTA in symptomatic patients with suspected CAD.13 The results of this study will be released in March 2015 and will likely provide further guidance on the most effective noninvasive approach to evaluating patients...
with chest pain. As a field, we must move beyond exclusively examining the necessary, but insufficient, metric of diagnostic accuracy and focus instead on the all-important goal of using noninvasive testing to improve patient outcomes.

Disclosures

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References


