Much of our training in imaging has historically focused on the detection and diagnosis of disease. We have strived for over one-half a century for greater sensitivity and accuracy. Unfortunately, despite our best intentions, this focus on accuracy has far too often led us on a path toward overdiagnosis of disease rather than enabling meaningful improvements in risk stratification and therapeutic decision making (1,2). Fryback and Thornbury (3) in their seminal paper highlighted the importance of thinking beyond disease detection and accuracy and reminded us to not test for the sake of testing but rather to help stratify risk and guide decision making that can afford improved clinical outcomes.

Over the last decade coronary computed tomography angiography (CCTA) has been validated as the noninvasive gold standard for the detection and exclusion of anatomical coronary artery disease, with several multicenter diagnostic accuracy studies particularly demonstrating high negative predictive value (4–6). CCTA has also been shown to provide robust prognostic information across a whole host of populations independent of traditional clinical risk assessment as well as help guide medical and interventional therapeutic decision making that can improve clinical outcomes in observational registries (7–10). Importantly, these findings have been shown in both women and men. However, while these data have helped us greatly understand the burden of disease and risk associated with it in modern populations of low-intermediate risk patients, these data have been only observational in nature and often limited to experienced centers. In the recently published PROMISE (Prospective Multicenter Study for Evaluation of Chest Pain) trial (11) over 10,000 subjects presenting with chest pain were enrolled and randomized to either a traditional stress testing strategy versus a CCTA strategy. The results of this trial highlighted the clinical value of CCTA as a viable alternative to stress testing. In fact, although there was equipoise in clinical outcomes at 2 years, those patients who randomized to the CCTA arm realized a significant reduction in major adverse cardiovascular events at 1 year ($p = 0.04$).

In this issue of the Journal, Pagidipati et al. (12) build on this seminal work through their subanalysis of the prognostic value of CCTA and stress testing stratified by sex. The findings suggest that the different testing algorithms result in different rates of test positivity and prognostic value between men and women.

After adjusting for clinical variables, women were more likely to have a positive stress test (exercise electrocardiography and technetium Tc 99m sestamibi but not stress echo) than a positive CCTA (odds ratio: 0.67; 95% confidence interval [CI]: 0.55 to 0.82). On the other hand, men were more likely to have a positive CCTA (odds ratio: 1.79; 95% CI: 1.45 to 3.04) than a positive stress test (stress electrocardiography and echo but not technetium Tc 99m sestamibi).
Importantly, a positive CCTA was associated with a much stronger hazard for downstream clinical events than a positive stress test in women (CCTA adjusted hazard ratio [HR]: 5.86; 95% CI: 3.32 to 10.35; stress adjusted HR: 2.27; 95% CI: 1.21 to 4.25). Conversely, in men, there was no significant difference in the risk of downstream events associated with a positive stress test or CCTA (CCTA adjusted HR: 2.80; 95% CI: 1.76 to 4.45; stress test adjusted HR: 4.42; 95% CI: 2.77 to 7.07; adjusted p = 0.168). Interestingly, stress testing and CCTA conferred similar negative likelihood for a downstream event in men and women. The authors posit that the superiority of CCTA in women may reflect a higher likelihood of false positive stress tests in women (with regard to obstructive epicardial coronary artery disease) than in men, thereby lowering the prognostic value of stress testing in women.

Although an extremely informative analysis, the data presented leaves many outstanding questions. As Pagidipati et al. highlight, as a pragmatic randomized trial, downstream treatment decision making was left at the discretion of the local practitioner. We are not provided with any information on downstream medical therapy or revascularization that could significantly impact clinical outcomes. This would be of particular interest in this analysis owing to the well-established sex-related treatment bias. In addition, given the modest number of clinical events and the pragmatic nature of this trial including multiple noninvasive ischemia tests to which patients were not randomized, Pagidipati et al. are unable to assess any potential differences in prognostic value between the different stress testing modalities used. Finally, although Pagidipati et al. suggest that negative stress tests and CCTA were equally likely to predict an event in both men and women, the relatively short-term follow-up is a significant limitation. It is well established that negative/normal non-invasive ischemia tests confer a good prognosis but the warranty period is consistently modest (approximately 2 years) (13). CCTA, on the other hand, is uniquely able to detect early disease confined to the wall of the coronary arteries long before there is an anatomical stenosis (14). As such, an unremarkable CCTA means that there is not only no stenosis but that there is no CT discernible atherosclerosis. This ability to exclude even mild forms of coronary artery disease has enabled a much longer warranty of a negative CCTA across many registries and studies. In fact, the warranty period of a negative CCTA is said to be at least 5 years. Given these differences in the warranty period in other observational studies longer-term follow-up of this large randomized cohort would be very helpful to inform the field about the relative prognostic value of a negative CCTA and stress test, both in the overall population and stratified by sex.

With increasing awareness of the importance of personalized medicine, we can no longer use the same diagnostic algorithms across all patient populations. In the end, although limitations remain, Pagidipati et al. should be commended for this important analysis, which serves to highlight the importance of understanding sex differences when developing diagnostic pathways. The stratification by sex and over a relatively short-term follow-up is only the beginning. We need longer-term data and we need to stratify further based on age and ethnicity among other variables to help harness the valuable information provided to us through our modern diagnostic tests. In addition, with the evolution of deep machine learning algorithms we will undoubtedly be able to uncover much more information and many more interactions that the human eye and mind are incapable of identifying. In the meantime though we should apply the important findings presented by Pagidipati et al. to better inform our diagnostic decision making and strongly consider the use of CTA in all patients with stable chest pain. In fact, I would argue that the data provided further support CCTA as the appropriate first-line test for women with new onset stable symptoms.

REFERENCES

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