Continuous improvement is better than delayed perfection.

—Mark Twain

The evaluation of patients with suspected but not yet confirmed of coronary artery disease (CAD) has become increasingly complex in the past decade.1 Multiple noninvasive modalities are now available with individual strengths and weaknesses. Decision making on noninvasive testing when evaluating stable chest pain is further complicated by the observed sex disparity in the clinical presentation, risk factors, and varied role of microvascular dysfunction.2

See Article by Penagaluri et al

Coronary computed tomographic angiography (CCTA) is an excellent tool in the exclusion of CAD with unparalleled diagnostic performance3–5 and provide valuable prognostic information.6,7 However the utility of CCTA continues to have 2 important limitations: (1) low specificity in the presence of CAD and (2) lack of lesion-specific physiological assessment. More recently, the introduction of myocardial CT perfusion imaging (CTP) has been shown to augment the information provided by CCTA alone by providing a physiological measure of the significance of a coronary artery stenosis. In the multicentered CORE320 trial (Computed Tomography Angiography and Perfusion to Assess Coronary Artery Stenosis Causing Perfusion Defects by Single Photon Emission Computed Tomography), a combined CCTA-CTP strategy significantly improved the specificity of CCTA alone from 54% to 73%, using invasive coronary angiography and single photon emission CT as the reference standard.8

In this issue of Circulation: Cardiovascular Imaging, Penagaluri et al9 performed an important subanalysis of the CORE320 trial evaluating the diagnostic performance of CCTA-CTP strategy stratified by sex. Interestingly, CTP provided a significant improvement in the discrimination of ischemia in women but not in men (AUC, 0.92 for CCTA-CTP versus 0.83 for CCTA alone for women; P=0.03 and 0.84 for CCTA-CTP versus 0.82 for CCTA alone for men; P=0.29). The difference in diagnostic performance is predominantly driven by the difference in specificity of CCTA and CCTA-CTP between the 2 sexes. With CCTA alone, the specificity for lesion-specific ischemia (defined as stenosis of >50% on invasive coronary angiography with corresponding area of perfusion defect on single photon emission CT) was 0.38 for men and 0.68 for women. Although there is an improvement in the specificity with the addition of CTP, an impressive difference between the 2 sexes persisted (0.44 for men and 0.74 for women; P<0.001). This analysis represents an important next step, as we strive for more personalized medicine approaches, to help understand what, if any, the role CTP has in men and women.

The disparate diagnostic performance characteristics can be explained at least, in part, by many mechanisms. One possible explanation is that this may reflect the difference in microvascular status in the setting of obstructive CAD between men and women. Microvascular dysfunction is more prevalent in women than in men,10 and women are therefore more likely to have abnormal myocardial perfusion detectable by CTP and single photon emission CT, which is not otherwise detectable by CTA or invasive coronary angiography.11 In addition, the microvasculature is also known to remodel in response to obstructive epicardial disease.12 As such, in the presence of obstructive epicardial disease, women are more prone to developing microvascular dysfunction when compared with men, potentially resulting in a greater likelihood of a true-positive CTP and single photon emission CT in women. This may, therefore, help explain the observed improved diagnostic performance of CTP over anatomic testing alone in women with little incremental value of CTP in men.

Although an interesting and important subanalysis, there are some salient limitations that should be highlighted. First, the population studied is at higher risk than those routinely being evaluated by CTA and CTP in that these patients were already referred for invasive coronary angiography. Second, the overall cohort is an imbalanced one with two third being men, thereby limiting the power of the analysis. Third, the relatively small cohort precluding caliper matching of men and women leaving a whole host of confounders with significant differences in baseline risk and symptom status between men and women. Women were younger, less likely to smoke, and less likely to have previous myocardial infarction. To illustrate the potent impact of these confounders on the interpretation of the result, during CCTA’s infancy, nonobstructive disease found on CCTA was thought represent higher adverse cardiovascular event rates in women than in men.13 However, when
patients were matched for age, cardiovascular risk factors, and angina typicality, the apparent sex disparity is no longer present and the extent and severity of CAD translate to equal prognostic value in both men and women.14

Finally, as the authors have highlighted, the study was not primarily designed to address the sex differences in the performance of CTP. Consequently, many of the nontraditional risk factors known to be associated with CAD in women such as menopausal status and estrogen receptor status were not prospectively collected, thereby limiting the opportunity to learn further about the potential role such factors may have in the development of CAD and ischemia in women. Notably, of the sex-specific risk factors suggested by the authors, estrogen status and possible supplementation is an omnipresent risk factor for all women evaluated and has previously been found to play a role in the development of CAD.15 Furthermore, at the molecular level, estrogen receptor expressions in human coronaries have been found to correlate to coronary calcium content and atherosclerotic plaque load and signal through pathways associated with microvascular dysfunction and atherosclerosis.16,17 This suggests that incorporating female-specific risk factors in future studies may be of value and elucidate novel aspects of ischemic heart disease in women.

Although recognizing these limitations, which are inevitably shared by any subanalysis of an accuracy trial, it is perhaps more important that as a field we focus more on where we need to take CTP and our diagnostic imaging paradigms. Accuracy is the first step in introducing a new imaging modality. There is much more that are needed to help clarify the role of CTP in the diagnosis and management of patients with suspected stable CAD. We, of course, do not pick imaging tests solely on the basis of its performance characteristics and certainly not when applied to different patient population. We image to help inform clinical decision making that enables an improvement in clinical outcomes in the way CCTA has contributed to the evaluation of patients with stable chest pain as shown in the recent PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain)18 and Scottish SCOT-HEART (Computed Tomography of the HEART)19 trials. To date, we lack any clinical utility data for CTP and therefore raise multiple unanswered questions: (1) Does CCTA-CTP provide incremental prognostic information beyond CTA alone? (2) Does it help guide revascularization beyond anatomy alone? (3) Can it better discriminate as to which patients are better served with an invasive strategy versus medical therapy? (4) Will it allow for a reduction in downstream ancillary testing? And finally, (5) Will it be a practical and cost effective tool to augment the management of patients after the diagnosis of anatomic disease on CTA?

It is important for us to build on these impressive accuracy data and design the necessary trials to define the clinical utility of CTP in this era of declining healthcare resources and under the auspices of comparative and cost effectiveness. As Penagalaru et al9 highlighted, given the varied manifestation, drivers of CAD in men and women and the possible sex disparity in the utility of CCTA-CTP, these questions will almost certainly need to be considered separately in women and men.

In the era of personalized medicine and limited resources, CCTA-CTP represents another step forward in the continuous improvement in the evaluation of CAD. Penagalaru et al9 performed an important subanalysis, illustrating a possible sex disparity in the diagnostic performance of CCTA-CTP. Although the study has its limitation, the direction in which this article represents is vitality important, and that is to strive toward an everimproving personalized medicine.

Disclosures

Dr Leipsic serves as a consultant and has stock options in Heartflow. S.H. Kueh received New Zealand Heart Foundation Fellowship Grant.

References


Developing a Deeper Understanding of Sex Differences in the Diagnostic Performance of Computed Tomographic Perfusion Imaging Toward a More Personalized Approach
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