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EDITORIAL COMMENT

Explanation of Sex Differences in Coronary Artery Disease

Finding Nemo?*

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Disentangling unique anatomic (eg, smaller coronary blood vessels) and physiological (eg, higher resting coronary blood flow) characteristics attributed to sex differences in atherosclerosis has been the focus of much research yet the encapsulation of diverse patterns that drive atherogenesis and acute coronary syndromes between women and men has remained elusive. In this issue of the *JACC: Asia*, Kim et al[1] are to be lauded for performing sophisticated analyses examining the interaction between characteristics of nonobstructive and obstructive atherosclerosis with physiological measures of vessel-specific ischemia (ie, fractional flow reserve [FFR]) and myocardial mass (ie, the substrate for demand) from noninvasive coronary computed tomographic angiography. In this cohort, women were older by 5 years with a similar burden of obstructive stenosis (mean stenosis = 46%; $P = 0.92$) even though the measurements of vessel diameter and lumen volume were significantly lower in women as compared with men. Despite the similar burden of coronary artery disease, including by vessel type and location, the investigators reported a higher (average) FFR value in women as compared to men. Fewer women had functionally significant (FFR ≤0.80), and intermediate stenosis as compared with men. These findings of a higher FFR have been previously reported.[2,3] The commonest explanation for the reported higher FFR values in women includes coronary microvascular dysfunction, the condition wherein a diminished hyperemic response could result in lower flow across the stenosis.[4] Coronary microvascular dysfunction does occur with and without obstructive coronary artery disease and, as such, this remains a plausible explanation for a cohort with men and women having a similar burden of obstructive stenosis. An even simpler explanation may be related to visual estimation of stenosis in a smaller coronary vessel, which may impact accuracy of the stenotic measurement in women as compared with men.

These investigators pursued a novel analysis to unearth sex differences in FFR based on variability in atherosclerosis interacting with myocardial mass.[5] They performed multivariable modeling and ascribed higher FFR values among women to their small left ventricular mass along with a lower plaque volume and fewer markers of high risk atherosclerotic plaque (ie, low attenuation plaque and positive remodeling) when compared with the male counterparts, as similarly reported in the CREDENCE (Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia) trial.[6] It has been proposed that the smaller myocardial mass would accordingly have a smaller vascular territory and potentially less flow into the subtended myocardium.[7] Interestingly, in multivariable modeling, female sex was not an independent predictor of FFR after covariate adjustment for stenosis severity, plaque morphology, and myocardial mass. These data suggest that sex differences in FFR relate to both vessel and myocardial factors—2-hit forces—and underscore the importance of interaction effects impacting women and men.

Importantly, for this comparison and for many more, the defining of a clear phenotypic pattern unique to women is complicated by age comparisons vetting older women against younger men. It is well

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established that the incidence of atherosclerosis rises dramatically among women following menopause, and this leads many to justify comparisons of women of advanced age to younger men. However, it also remains likely that comparisons of atherosclerotic plaque capture women and men at differing stages of early as compared with more advanced atherosclerosis. In the current cohort by Kim et al,[1] they in fact compare women and men with similar degree of stenosis severity, and as such, this in part equilibrates the challenges often noted in other series. However, the volume of atherosclerosis and ensuing high-risk plaque features were significantly less in women vs men, thus leaving open the potential for comparisons by sex, which are flawed by temporal inequality in atherogenesis. Not only the timing is in question, but the rapidity or rate of progress from initial disease onset to the manifestation of symptoms and acuity of presentation may be variable. This statement is by no means a criticism of the Kim et al[1] report, as we know very little about disease onset and progression, let alone the nature of variation by sex. Two additional challenges including prominent environmental interactions remain, which further complicate noteworthy differences between women and men, especially as it relates to the presence of cardiac risk factors, such as hypertension. Finally, the higher FFR values for a similar burden of coronary artery disease could be attributed to a chance finding or to selection bias, as these women may have had a varied evaluation pathway leading to coronary computed tomographic angiography.

This analysis is consistent with many other research endeavors from this investigative group in that the study is very well conducted and provides novel insight into observed differences in FFR between women and men. As the investigators note, several studies found *nemo* and failed to reveal sex differences in coronary artery disease. They reiterate we must not dismiss the existence of fundamental differences between women and men. The loss of endogenous estrogen and the marked increase in cardiovascular risk associated with menopause in women fundamentally underlies differences between the sexes.[8]

As aptly believed, the mark of an outstanding report is that it leaves you asking many questions but also unfolds numerous potential pathways for further research. The current investigation has invoked hitherto uncharted mechanisms in the topic of critical differences in the pathophysiology of coronary artery disease in women as compared with men.

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