JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 4, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.02.016

EDITORIAL COMMENT

Correlation Among Coronary CT Findings, Sex, and Events

Should We Wait to CONFIRM?*

Kim Allan Williams, Sr, MD,[a] Sarah Alexander, MD[b]

The significance of ischemic heart disease (IHD) in women was brought to the forefront nearly a decade ago with the realization that more women than men were dying from cardiovascular disease (CVD). In response, the American Heart Association (AHA) convened the Go Red For Women campaign to raise awareness of heart disease in women and to empower women to know their risk for CVD and take action to reduce their risk. Along with a call to action for patients, research was undertaken to investigate the sex differences in IHD, particularly in the management and outcomes of CVD. Women are known to have less obstructive coronary artery disease (CAD), yet they tend to experience more symptoms, hospitalizations, and adverse outcomes than men, as seen in the WISE (Women's Ischemia Syndrome Evaluation) study (1). Sex differences in the pathophysiology of IHD have been characterized, including more microvascular coronary dysfunction and different mechanisms of acute coronary syndrome (ACS) development: plaque "erosion" (more commonly seen in younger women and premenopausal smokers) versus plaque "explosion" (the typical mode in men) (1,2). Public awareness campaigns and sex-focused research were an effort to decrease CVD in women, as heart disease has consistently been the number 1 cause of mortality in both women and men in the United States (3) and now globally (4).

The recent Heart Disease and Stroke Statistics—2016 Update published by the AHA provided much encouragement to providers of cardiovascular care for women: "For the first time since 1983, more males (402,851) died of CVD than females (398,086)" (5). Although the 2016 update provides hope that public campaigns and research have yielded a tangible impact on CVD mortality in women, more inquiry is needed with regard to evaluation and management of CVD in women. With the emergence of multimodality imaging and the movement to more noninvasive assessment of coronary disease in patients, rapidly evolving imaging modalities should be examined for their prognostic value in both men and women.

Over the past few years, coronary computed tomography angiography (CTA) has developed as a method to noninvasively assess the anatomic presence and functional significance of CAD. The presence of obstructive CAD as detected on coronary CTA has been associated with increased risk of mortality and major adverse cardiac events (MACE) in multiple studies (6–8), but these studies were limited by short-term follow-up, small patient cohorts, and single-center observations. The CONFIRM (Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry was designed as an international, multicenter observational study to prospectively follow patients who had undergone coronary CTA and to determine the prognostic value of coronary CTA findings and prediction of future adverse events (9). In this issue of *iJACC*, Schulman-Marcus et al. (10) studied a cohort of 5,632 patients from the CONFIRM registry, of whom 36.5% were women, to determine whether there is a sex-specific relationship between extent of CAD and risk of MACE over a 5-year period of follow-up. The primary outcome measure was MACE defined as a composite of all-cause mortality and nonfatal myocardial infarction (NFMI) while secondary outcomes measured were all-cause mortality and NFMI. The authors found a dose response relationship between CAD extent and MACE risk with increasing number of vessels with obstructive CAD corresponding to an increased MACE risk.

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the [a]Division of Cardiology, Rush University Medical Center and Rush University School of Medicine, Chicago, Illinois; and the [b]Division of Cardiology, Department of Medicine, Rush University Medical Center, Chicago, Illinois. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

JACC: CARDIOVASCULAR IMAGING, VOL. 9, NO. 4, 2016
APRIL 2016:373–5

The graded increase in MACE risk was seen in the overall cohort as well as in women and men. Additionally, there was a stepwise increase in the secondary outcome of NFMI associated with increased per-vessel CAD extent. In their study, Schulman-Marcus et al. (10) conclude that there is no significant observed interaction of sex between MACE and increasing per-vessel extent of obstructive CAD.

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The results are clear that coronary CTA retains prognostic significance with regards to predicting MACE and NFMI in both women and men, which is reassuring to the clinician when evaluating study results. However, in this age of cardiology where there are multiple options for diagnostic testing coupled with a call for increased cost and radiation consciousness and physician reporting of patient outcomes, we would be interested to know how the coronary CTA results influenced medical therapy. As the finding of nonobstructive CAD was associated with increased MACE risk in both sexes, it would have been helpful to analyze the clinical response to the coronary CTA findings, as the authors acknowledge. The addition of or intensification of medical therapy with statins, aspirin (ASA), and/or lifestyle changes may have changed the outcome for many patients, unless these findings were deemed insignificant and no subsequent changes were undertaken. We suspect that the presence of CAD on coronary CTA would lead to intensification of medical therapy as shown by Hulten et al. (11). In that study, the severity of CAD seen on coronary CTA was associated with subsequent increased statin and ASA use, which led to a significant decline in low-density lipoprotein levels. Moreover, they showed that statin use in those patients with extensive, non-obstructive CAD was associated with a significant reduction in cardiovascular death or myocardial infarction (11).

Interpretation of coronary CTA findings in the context of sex and changes in downstream medical therapy would be informative. Despite the data showing increased incidence of MACE, is the finding of nonobstructive CAD in women viewed differently than the same finding in men? Interestingly, in the CONFIRM cohort, women were older than men, had a higher incidence of hypertension (HTN), and were less likely to be taking ASA. Multivariate analysis showed that use of angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker therapy at baseline was associated with MACE. Was the latter finding due to the presence of underlying congestive heart failure, or was it due to the severity of HTN? Notably, HTN was indeed associated with MACE in MVA. Understanding that the adjudication of post-coronary CTA medical therapy is limited by the international nature of the CONFIRM registry and, therefore, differences in standards of care and clinical practice, this leaves space for future studies examining the effect of coronary CTA findings on medical decision making (both medical therapy and referral to invasive coronary angiography) when taking into account sex.

Beyond anatomic information, coronary CTA can also be used to evaluate the functional significance of visualized plaque. This would be helpful in understanding the increased MACE risk associated with non-obstructive CAD, which is more prominent in women. Prior research has shown that positive vascular remodeling and low attenuation plaque are characteristics of culprit lesions in ACS (12). These features, along with others such as spotty calcification and “napkin-ring” stenoses, should be pursued to determine if there are sex-specific, high-risk plaque characteristics that would encourage primary prevention strategies.

Previous investigations have demonstrated sex differences in the pathophysiology of IHD, and the current study by Schulman-Marcus et al. (10) shows that coronary CTA detection of CAD extent retains prognostic significance in both sexes. In the current transformation of patient care from “volume to value,” effective use of tests and institution of therapies known to improve outcomes and reduce mortality has become paramount. Central to this focus is ensuring that patients are treated appropriately for their event risk and that preventive measures are underscored. Therefore, evaluating for possible differences in post-coronary CTA medication management between sexes and determining sex-specific plaque features detected on coronary CTA can help clinicians develop targeted treatment plans.

In sum, we applaud the authors of the CONFIRM study for setting up an excellent template from which to take a deeper dive into issues such as using noninvasive imaging, not just to detect but to risk-stratify and guide preventive therapy. Future studies could address 2 lingering questions: can interventions based on coronary CTA findings decrease the frequency of MACE for both sexes, and are there sex-specific, high-risk plaque characteristics that can differentially predict increased risk of MACE? We eagerly wait to CONFIRM.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Kim Allan Williams, Sr., Division of Cardiology, Rush University Medical Center, 1717 West Congress Parkway, Suite 303 Kellogg, Chicago, Illinois 60612. E-mail: Kim_A_Williams@rush.edu.

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KEY WORDS CAD, CT coronary angiography, sex differences