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

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.02.014

EDITORIAL COMMENT

Similar Plaque Composition in Men and Women With Stable CAD

Another Myth Falls*

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Risk stratification, diagnostic work-up, treatments, and prognostic evaluation of coronary artery disease (CAD) in women represent the adaptation of the vast knowledge modeled for male CAD in the last 50 years: this is proven by the low proportion of women included in past clinical studies (1). After publication of sex-specific clinical recommendations for the prevention of cardiovascular diseases (2), awareness, risk stratification, treatment and prevention of cardiovascular disease in women improved: women are now being more represented in emerging studies addressing risk profile, plaque burden, complications, and management of CAD.

Acute and chronic ischemic heart disease (IHD) is uncommon in pre-menopausal women. After menopause and with ageing, the prevalence, risk stratification, and events tend to equalize in the sexes. Several past assumptions about female CAD are evolving. Although angina remains the most common first presentation of disease among women (3) prevalence of acute coronary syndromes (ACS) has increased in young women and declined in age-matched men (4). Risk factors such as diabetes and hypertension are more common in women than in men (5). However these risk factors are associated with nonproportional effects in women (6). Plaque burden is lower in women than in men (7), and plaque composition shows lower prevalence of mixed plaques (8). Plaque complications differ in the sexes: erosions underlying thrombosis in fatal ACS (9) is more common in women than in men. As in vivo studies show that culprit lesions with intact fibrous cap are associated with better long-term prognosis than those with plaque rupture (10), autopsy and clinical series may not fully coincide. In vivo imaging studies exploring plaque morphology are now uniquely contributing to characterize atherosclerotic plaques in acute and chronic CAD (11,12).

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PLAQUE COMPOSITION IN STABLE CAD LOOKS SIMILAR IN MEN AND WOMEN

In this issue of *iJACC*, Bharadwaj et al. (12) report data from 383 patients with stable CAD who were referred for angiography and underwent optical coherence tomography (OCT); 128 of 382 patients also underwent intravascular ultrasonography (IVUS)/near infrared spectroscopy (NIRS). The study included 268 men and 115 women. The risk profile in women was higher than in men: women were older and had more hypertension, insulin dependent diabetes, and obesity. OCT did not show sex difference in plaque morphology, lipids, thin cap fibrous atheroma, microvessels, macrophages, and plaque calcifications; NIRS did not demonstrate differences in maximal lipid core burden index at the 4-mm maximal segment. IVUS showed similar plaque characteristics in men and women, except for an increase in plaque burden in the reference segment ($p = 0.031$). Sex was not an independent predictor of severe plaque burden by IVUS (12). On the basis of their results, the authors (12) suggest equally aggressive primary and secondary preventive efforts regardless of sex, especially considering the known undertreatment of women with stable angina and angiographically significant disease (13) and their higher coronary atheroma regression when treated with statins (14). The merit of the study is in

*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.

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addressing stable CAD in women and using multimodality intravascular imaging to evaluate sex differences; the limitations are the retrospective study and disparity in the number of cases investigated with different imaging modalities. However, the new message is that plaque burden and composition do not differ in men and women with stable CAD. At a time when the role of thin cap fibroatheroma as a cause of ACS is losing importance due to the notion that plaque erosion is probably more common than expected, the finding of similar plaque burden, morphology and composition in stable CAD of men and women, encourages the development of novel models of research that should specifically focus on female CAD.

RESEARCH OF CAD IN WOMEN: FROM CONVENTIONAL TO SEX-SPECIFIC RISK FACTORS

The comparative strategy of research of CAD (men vs. women) reduces the investigation of risk factors to those that are shared by the sexes. This prevents the expansion of investigation of female-specific risk factors such as autoimmune diseases, thyroid dysfunction, and hormone- and pregnancy-related risk (15). The higher prevalence of chronic inflammatory and autoimmune diseases in women is proven: in women with rheumatoid arthritis, systemic sclerosis, systemic lupus erythematous, CAD is recurrently described as a form of "accelerated atherosclerosis" that leads to premature clinical manifestations and events and is independent of the presence or absence of traditional risk factors for CAD; when present, traditional risk factors worsen the disease, but their absence does not exclude the occurrence of "accelerated CAD" (16). Thyroid diseases, both manifest and subclinical hypothyroidism, are common in women and are associated with endothelial dysfunction and increased risk of CAD (17). Reproductive factors such as later age at menarche, increased number of pregnancies, shorter lactation time, gestational diabetes, and pre-eclampsia are sex-specific risk factors for CAD (15,18). Research on CAD in women would probably benefit from comparative studies in subgroups of affected vs. non-affected women, or women carrying known risk factors vs. sex-specific factors.

IMAGING MODALITIES AND CAD IN WOMEN. Beyond coronary angiography, which remains the gold standard for routine assessment of CAD and for interventional procedures in both acute and chronic coronary syndromes, intravascular and noninvasive coronary imaging are contributing to highlight similarities and differences of morphology and complications of coronary plaques in men and women. Bharadwaj et al. (12) used OCT, IVUS, and NIRS in patients with stable CAD. With a resolution ranging between 100 and 150 μm, IVUS provides information on luminal border, plaque morphology, plaque burden and plaque composition, media-adventitia interface, and remodeling (19). The only difference identified by Bharadwaj et al. (12) in male and female series was the increase in plaque burden in the reference segment (16).

With a resolution of 10 to 15 μm, frequency domain-OCT provides detailed description of superficial and intermediate plaque layers; the penetration is lower than that of IVUS and the information on plaque burden is limited. However OCT can detect small pultaceous cores and fibrous components and characterizes the superficial layers of the plaque including cap rupture (20). In their series of patients with stable CAD, Bharadwaj et al. (12) observed plaque rupture and thrombus in 14% and 9% of male patients and 10% and 8% of female patients, respectively.

PERSPECTIVES

Intravascular imaging is expanding our understanding of pathological morphology of coronary plaques in ACS and now also in chronic CAD. Multiple imaging modalities integrate information from tools that differently explore superficial or deep plaque layers, plaque burden and composition, and vessel wall remodeling. Comparative invasive studies are unlikely to enroll age-matched patients because clinically manifest CAD develops 7 to 10 years later in women than in men. Serial data are now achievable with noninvasive imaging such as multidetector computed tomography coronary angiography (MD-CTCA) in high-risk cohorts of individuals in the pre-symptomatic phases of CAD (21). MD-CTCA identifies, characterizes, and quantifies obstructive and nonobstructive coronary plaques. MD-CTCA-based studies can enroll equal proportions of age-matched women and men who share the same risk profiles or subgroups of women with sex-specific risk factors; they also provide further and earlier exploration of asymptomatic CAD and comparison of data are achievable with invasive intravascular imaging in symptomatic patients. Noninvasive imaging of coronary arteries is feasible and sustainable and represents the novel avenue for early pre-clinical diagnosis of CAD.

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REFERENCES

1. Tsang W, Alter DA, Wijeysundera HC, Zhang T, Ko DT. The impact of cardiovascular disease prevalence on women's enrollment in landmark randomized cardiovascular trials: a systematic review. J Gen Intern Med 2012;27:93–8.

2. Mosca L, Benjamin EJ, Berra, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update. A guideline from the American Heart Association. Circulation 2011;123:1243–62.

3. Kannel WB, Feinleib M. Natural history of angina in the Framingham study. Prognosis and survival. Am J Card 1972;29:154–63.

4. Towfighi A, Zheng L, Ovbiagele B. Sex-specific trends in midlife coronary heart disease risk and prevalence. Arch Intern Med 2009;169:1762–6.

5. Anand SS, Islam S, Rosengren A, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J 2008;29:932–40.

6. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73–8.

7. Rodriguez K, Kwan AC, Lai S. Coronary plaque burden at coronary CT angiography in asymptomatic men and women. Radiology 2015;277:73–80.

8. Qureshi W, Blaha MJ, Nasir K, Al-Mallah MH. Gender differences in coronary plaque composition and burden detected in symptomatic patients referred for coronary computed tomographic angiography. Int J Cardiovasc Imaging 2013;29:463–9.

9. Yahagi K, Davis HR, Arbustini E, Virmani R. Sex differences in coronary artery disease: pathological observations. Atherosclerosis 2015;239:260–7.

10. Yonetsu T, Lee T, Murai T, et al. Plaque morphologies and the clinical prognosis of acute coronary syndrome caused by lesions with intact fibrous cap diagnosed by optical coherence tomography. Int J Cardiol 2016;203:766–74.

11. Jia H, Abtahian F, Aguirre AD, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. J Am Coll Cardiol 2013;62:1748–75.

12. Bharadwaj AS, Vengrenyuk Y, Yoshimura T, et al. Multimodality intravascular imaging to evaluate sex differences in plaque morphology in stable CAD. J Am Coll Cardiol Img 2016;9:400–7.

13. Daly C, Clemens F, Lopez Sendon JL, et al. Gender differences in the management and clinical outcome of stable angina. Circulation 2006;113:490–8.

14. Puri R, Nissen SE, Shao M, et al. Sex-related differences of coronary atherosclerosis regression following maximally intensive statin therapy: insights from SATURN. J Am Coll Cardiol Img 2014;7:1013–22.

15. Gill SK. Cardiovascular risk factors and disease in women. Med Clin North Am 2015;99:535–52.

16. Kivity S, Ehrenfeld M. Can we explain the higher prevalence of autoimmune disease in women? Expert Rev Clin Immunol 2010;6:691–4.

17. Grais IM, Sowers JR. Thyroid and the heart. Am J Med 2014;127:691–8.

18. Harvey RE, Coffman KE, Miller VM. Women-specific factors to consider in risk, diagnosis and treatment of cardiovascular disease. Womens Health 2015;11:239–57.

19. Zheng B, Mintz GS, McPherson JA, et al. Predictors of plaque rupture within nonculprit fibroatheromas in patients with acute coronary syndromes: The PROSPECT study. J Am Coll Cardiol Img 2015;8:1180–7.

20. Niccoli G, Montone RA, Di Vito L, et al. Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. Eur Heart J 2015;36:1377–84.

21. Fordyce CB, Newby DE, Douglas PS. Diagnostic strategies for the evaluation of chest pain: clinical implications from SCOT-HEART and PROMISE. J Am Coll Cardiol 2016;67:843–52.

KEY WORDS intravascular imaging, intravascular ultrasound, optical coherence tomography, plaque morphology, sex