



Sex differences in the manifestation and evolution of coronary artery plaques

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Editorial

Even though the past decades have brought an increase in the understanding of the pathophysiology of coronary artery disease (CAD), several aspects remain incompletely understood. This is especially true for sex-specific differences in the development, manifestation, and prognosis of coronary artery plaques. While the prevalence of obstructive CAD is higher in men compared to women, non-obstructive CAD and ischemia with no obstructive coronary arteries (INOCA) are relatively more common in women [1–3]. Compared to obstructive CAD, fewer established preventive, diagnostic and treatment options are available for INOCA [4], complicating treatment of CAD, especially in younger women at low cardiovascular risk. Atypical symptoms in the clinical setting of suspected CAD are more common in women than in men, which might lead to delayed detection of CAD and acute coronary syndrome [5]. Women present with the disease at higher age [6] and are at higher risk for major adverse cardiovascular events and fatal outcome of myocardial infarction compared to men in the presence of obstructive, and as well in non-obstructive CAD [5, 7–9]. Sex-dependent disparities seem to diminish when women reach menopause and similar CAD prevalence rates and mortality rates in patients with myocardial infarction are observed in the seventh decade of life for men and women [8, 9].

Several models were established to explain these findings and encompass sex-specific exposure to cardiovascular risk factors (CVRF), differences in the pathophysiology of plaque formation, and the protective impact of estrogen. Beyond traditional CVRF, several sex-specific risk-enhancing conditions may be present in women: the higher prevalence of depression in women, pregnancy-associated

disorders like preeclampsia or gestational diabetes mellitus and arterial hypertension, delivery of a low-birth weight infant, pregnancy-associated cessation of statin intake, and premature menopause [10–12]. Loss of the ovarian function and the protective effect of estrogen after menopause may foster activation of the renin–angiotensin–aldosterone system, left ventricular remodeling, and endothelial dysfunction [13]. Furthermore, estrogen-mediated effects on the lipid- and cholesterol metabolism of the liver are proposed to modify the cardiovascular risk [14]. Although these findings implicate a cardioprotective effect of estrogen, hormone replacement therapy has failed to modulate the progression of CAD in postmenopausal patients [15, 16]. The interaction of hormones, traditional CVRF, and risk-enhancing conditions seems to be more complex than assumed and further evidence on sex differences in the pathophysiology of CAD is warranted. In this regard, the formation of atherosclerotic plaques and the change of plaque morphology over time is crucial to understand the evolution from asymptomatic non-obstructive CAD to acute myocardial infarction.

Previous studies could identify different characteristics of coronary artery plaques in men and women. Due to the heterogeneity between studies in terms of imaging modalities (invasive optical coherence tomography (OCT) [17, 18] versus invasive intravascular ultrasound (IVUS) [19–21] versus noninvasive imaging (i.e. coronary computed tomography angiography; CCTA) [1, 22–24]) and investigated lesions (non-obstructive or obstructive [1, 18, 23, 24] versus culprit lesions in myocardial infarction [17, 19]) results concerning sex-differences were incoherent. In patients undergoing CCTA, the following findings were consistent between most studies: Men have higher plaque burden in terms of number of plaques and plaque volume, obstructive disease is more common in men, and the relative number of non-calcified plaque is higher in women than in men [1, 22–24]. On contrary, OCT and IVUS findings suggest a higher prevalence of lipid-core plaques in men compared to women [18, 21]. Due to the invasive nature of OCT and IVUS, these findings

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might be related to the higher number of patients included with acute coronary syndrome compared to CCTA studies where mostly patients at low- to intermediate pretest probability for CAD were assessed. Although there exists evidence on sex-differences of coronary plaques, most studies were limited to a one-time point assessment of the plaque burden and hence their results only represent a snapshot in the continuum of CAD. So far, little is known about sex-dependent changes of coronary plaques over time in intermediate and low-risk patients.

In this context, we congratulate on the important presented study by El Mahdiui et al., which provides further insights into sex differences in the evolution of coronary plaques. The authors sought to analyze sex disparities in coronary plaque morphology changes by serial non-invasive imaging using CCTA in a low- to intermediate CAD risk population from the multinational, multicenter prospective SMARTool study (Simulation Modeling of coronary ARTery disease: a tool for clinical decision support).

In a total of 211 patients, recruited in seven centers of five European countries who underwent clinically indicated CCTA, after a mean time of about 6 years a second CCTA was conducted to assess changes in coronary plaque morphology. The main findings were that prevalence of coronary plaques and mean percentage fibro-fatty atheroma volume (PAV) were consistently higher in men than in women. In the subgroup analysis, where patients were dichotomized by age groups, a more pronounced regression of fibrous and non-calcified PAV in women under 55 years of age compared to age-matched men was revealed. No differences in the change of total or compositional PAV were observed between women and men of 55 years or older. The results implicate a possible association of plaque formation to estrogen levels, since regression of fibrous and non-calcified PAV was observed only in women expected to be premenopausal, but not in men or older women. Finally, the present study could confirm some general findings on sex disparities in CAD: women with CAD were older than men, had higher high-density lipoprotein (HDL) levels, and presented more often with atypical symptoms compared to men.

Strengths of the presented study are the multicentric design, the serial CCTA assessment over time, the interpretation of the CCTAs in a core laboratory and the long follow-up. Limitations are based on the fact that women were underrepresented (31%) which complicates the statistical comparison to the larger group of men and the nature of the study, which did not link changes in plaque morphology to clinical outcomes. Plaque burden is an important outcome predictor and findings on sex-discrepancy would have helped to understand the evolution from stable plaque to myocardial infarction in men and women. The proposed associations of plaque changes to menopause should be interpreted with caution since it was made on

the observation of differences between age-groups by a cut-off of 55 years. The presence of menopause is not an exclusively age-dependent variable and should have been determined by either standardized questionnaires or sex hormone levels, rather than stratified according to age-groups. Nevertheless, the finding is in line with previous studies, implicating a protective effect of estrogen. Sex differences in CAD remain a timely topic because the management of CAD in women is still suboptimal. Women with suspected CAD are less likely to be diagnosed early, receive less preventive care and are treated less adequately for CAD [6]. Patient education of women who are at high cardiovascular risk is worse compared to men and women are less aware of the fact that they are at high risk and hence present later at the emergency unit when they suffer from acute coronary syndrome [5, 25]. Modifiable risk factors explain 94% of the occurrence of myocardial infarction in women and preventive treatment is a powerful tool to improve survival [26]. Nevertheless, guidance on approaches to modify risk factors is often lacking in women [25]. The presented study showed sex-differences in the development of coronary artery plaques and promotes the establishment of sex-based management of CAD. Encouragingly, in recent years, awareness for sex-specific factors of CAD is rising in risk factor management, and recently published guidelines include sex-specific CVRF in the decision process for statin therapy [27]. However, the therapeutic implications of changes in non-obstructive plaque morphology in men versus women remain to be elucidated. There are no guidelines or consensus that specifically address possible treatment adaptation according to plaque morphology changes over time. Development of further sex-based management according to imaging-based findings should be pursued in the future to guarantee optimal tailoring of therapy for men and women with CAD.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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