Trends in Cardiovascular Medicine 29 (2019) 56–57

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Editorial Commentary: Complex interactions of age and sex on acute coronary syndromes☆

Melinda B. Davis, MD

1500 E Medical Center Drive, University of Michigan, Ann Arbor, MI 48109-5853, United States.

In the 1990s, the National Institutes of Health (NIH) issued a policy to ensure that women were included in clinical studies. In 2015, the NIH released the "Consideration of Sex as a Biological Variable in NIH-funded Research" which highlighted the expectation that sex and gender be considered in research design, analysis and reporting of results. The Sex And Gender Equity in Research (SAGER) guidelines give specific recommendations on how to include the influence of sex in clinical research [1]. Other organizations such as the American Heart Association, the Canadian Institutes of Health Research, and the European Commission have also called for sex and gender analysis in research [2,3]. Despite significant interest and enthusiasm to understand sex differences in acute coronary syndromes (ACS), many gaps in our knowledge remain. In particular, the complex interactions of age, biological sex, and gender often yield conflicting results.

In this issue of *Trends in Cardiovascular Medicine*, Bugiardini et al [4] outline many of the challenges in studying the effects of age and sex in ACS. Although ACS is less common among younger women, this group is at particularly high risk for adverse outcomes. Bugiardini and colleagues summarize several of their findings from the ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries) registry with a focus on this high risk population. They also highlight current limitations in the literature due to study design, methods of model adjustment, and definitions of young age and ACS.

Several studies have reported worse outcomes among younger women with ACS. Data from the National Registry for Myocardial Infarction showed that young women had twice the mortality rate as young men under age 50, with no differences in mortality after age 74 [5]. Young women<55 years in the GRACE registry were found to have higher rates of rehospitalization, but no increased in-hospital or short-term mortality [6]. More recently, an analysis from the ISACS-TC registry showed that after ACS, women<45 years had higher 30-day mortality than similar-aged men (OR 6.0; 95% CI 2.07–17.53), even after adjustment for medications and reperfusion therapy [7].

Treatment disparities may account for a portion of the adverse outcomes [5]. Delays to presentation and treatment, under-recognition of symptoms, less revascularization and less guideline-directed medical therapy have been reported in women. However, in one of the ISACS-TC registry papers on STEMI, even when women and men were balanced in terms of baseline characteristics, medication treatment, and time to presentation, young women continued to have higher mortality than young men (OR 1.49, 95% CI 1.15–1.92) [8].

Different cardiovascular risk profiles may selectively disadvantage women, including smoking and diabetes. Young people with ACS are more likely to have a family history of coronary artery disease and have more obesity and less hypertension, diabetes, and hyperlipidemia [6,7]. Young women have more diabetes and hypertension than young men [6]. Cardiovascular risk factors that are specific to women, including early menarche, polycystic ovarian syndrome, and pregnancy-related factors such as preterm delivery, gestational hypertension, preeclampsia, and gestational diabetes, are associated with increased future risk of CVD. Furthermore, depression, anxiety, and post-traumatic stress disorder are common in women and may be associated with coronary disease [3,9].

What is the pathophysiologic evidence that female sex is a biological variable? Differences in outcomes among young women may be related to vascular biological factors such as lower coronary flow reserve, more vascular stiffness, and functional differences of smooth muscle cells in the vessel wall [10]. Women are more likely to have endothelial dysfunction, microvascular disease, nonobstructive coronary disease, plaque erosion, and vasospasm. A recent study of sex hormone levels in post-menopausal women demonstrated than a more androgenic profile (higher testosterone/estradiol ratio) was associated with increased cardiovascular disease, coronary heart disease, and heart failure [11]. Since estrogen can induce vasodilation, inhibit the renin angiotensin system, and regulate inflammatory markers and cytokines, women who present with coronary disease in the premenopausal state may have more severe underlying susceptibility to coronary disease to have overcome the protective effects of estrogen.

In this review by Bugiardini et al. [4], several challenges in studying the role of age and sex are highlighted. Across studies, "young" age is defined differently. Similarly, while some studies group all types of ACS, others include only STEMI. Studies that rely on population-level aggregate data may not represent individual-level relationships, and statistical models vary significantly between studies.

Bugiardini et al. successfully raise awareness of the importance of studying sex as a biological variable. However, sociocul-

☆ **No disclosures**

E-mail address: davismb@umich.edu

https://doi.org/10.1016/j.tcm.2018.06.012

tural gender-related differences remain largely unexplored. *Gender* reflects social norms and roles ascribed to women and men. A study by Pelletier and colleagues [12] demonstrated that personality traits and social roles traditionally ascribed to women were associated with adverse cardiovascular outcomes in young patients with ACS. They found that personality traits, such as shyness and being sensitive to others, and social roles, such as being responsible for housework, increased the risk of adverse outcomes. Interestingly, in this study there were no differences in outcomes based on biological sex. More research is needed to explore the relative influence of biological sex versus the sociocultural, gender-related lived experience that impacts a variety of health behaviors.

In summary, recent studies have added to our understanding of sex differences in ACS and suggest that higher mortality persists among young women despite adjustment for treatment disparities. Future research should explore the following questions: (1) How can we improve our detection of pathophysiological differences such as endothelial and microvascular dysfunction and plaque morphology? (2) How can we better understand the complex interactions between biological sex and sociocultural gender roles? (3) Why are some risk factors more prevalent and more deleterious among women? (4) How can we use pregnancy-related risk factors to identify women at increased risk for cardiovascular disease and translate this into effective prevention? No single study can answer all these questions, but clearly, the complex interactions of sex and gender with cardiovascular disease represent exciting topics ripe for additional research.

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