



Editorial

Sex as a Key Variable in Predicting Cardiovascular Outcomes: Rapidly Evolving Knowledge but Much More Needed

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Men and women are different. That has been known as long as humankind has been around. However, it has taken longer for physicians and scientists to realize that beyond the obvious physical differences, there are major discrepancies between the sexes in cardiovascular disease presentation, pathophysiology, management, and outcomes.^{1,2} Some of the differences are due to sex-related factors, and others relate to gender-related factors due to societal expectations and differential environmental exposures.³ Although gender- vs sex-related determinants are often not well discriminated, both have major impacts that need to be considered in clinical decision making; however, there is a dearth of data to allow the effective generation of sex-related clinical management guidelines.⁴ Low participation of women in trials, an unfortunate tendency to assume superficially that drug and device safety and efficacy are the same in both sexes, lack of focus on sex-specific risk factors, and psychosocial determinants of health are among the many factors responsible for the insufficiency of data.

In light of increasing awareness of the importance of sex- and gender-related factors in clinical decision making, there has been a progressive increase in the volume of research in this area. Over the past few months, the *Canadian Journal of Cardiology* has received multiple high-quality clinical research articles dealing with the theme of sex as a predictor for cardiovascular outcomes, and we have decided to publish them in a single Focus Issue that highlights the importance of this area. The present issue is the fruit of that decision.

Sex as a Predictor of Outcomes in Heart Failure

In this issue, Cannata et al. evaluate the sex-dependence of prognosis among patients with dilated cardiomyopathy.⁵ They note that women with this diagnosis tend to be older and have more conduction disturbances along with ventricular dilation. However, on multiple variable analysis, the long-term prognosis was better for women than for men. This finding is consistent with previous work indicating that ventricular dilation predicts worse outcomes in men but not in women with acute heart failure (HF).⁶ In an accompanying editorial, Yogasundaram et al. comment on the importance of the Cannata et al. findings⁷ and emphasize the consistency with previous work showing male sex to be an adverse predictor in dilated cardiomyopathy.⁸

In a related study, Kajimoto et al. examine the predictive value of New York Heart Association (NYHA) functional class in acute HF patients.⁹ In HF with reduced ejection fraction, NYHA functional class IV was a significant negative predictor in women but not in men. On the other hand, NYHA functional class IV augured negative outcomes in HF with preserved ejection fraction for both sexes. In an accompanying editorial, Cai et al. emphasize the fact that women frequently receive less guideline-recommended therapy than men and that further research is needed to define outcome predictors in men vs women and to clarify underlying mechanisms.¹⁰

In contrast to the sex differences highlighted in the above studies, Vishram-Nielsen et al. found that the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) score outperformed the Seattle Heart Failure Model (SHFM) equally in both sexes, but both overestimated mortality in women.¹¹ In their editorial, Diamant and Toma emphasize caution in interpreting those results and the need to obtain specific data in vulnerable groups, including women, that would allow for group-specific risk scores to optimize

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evidence-based approaches.¹² This is likely to be particularly true of groups with combined vulnerabilities, such as indigenous women, whose rate of CVD is growing significantly, and gender-related characteristics such as poverty.¹³

Sex-Specific Risk Factors

Women are known to have less cardiovascular disease (CVD) as a function of age than men. However, Langlois et al. show that the age-dependent CVD risk of women with preeclampsia approaches that of men, removing some of their sex-related protection.¹⁴ Dayan and Udell raise the possibility that women with preeclampsia have a more “male” physiology than other women.¹⁵ They raise the interesting possibility that biologic sex might be more than a simple binary variable and emphasize that gender may play a role and was not considered in the Langlois et al. study. They also comment on the importance of developing better tools to allow sex-specific risk estimation and establishment of sex-specific targets. One can hope that better sex-directed risk prediction and management tools would help to reduce the excess out-of-pocket expenses incurred by women, particularly for cardiac rehabilitation, in the Canadian publicly funded health care environment.¹⁶ Male sex is a predictor of better cardiorespiratory fitness with cardiovascular rehabilitation,¹⁷ and improved delivery of cardiorespiratory rehabilitation to women is an important goal. Interestingly, women appear to benefit from heart transplantation as well as men in terms of cardiorespiratory fitness, yet only one-third of patients undergoing heart transplantation are women.¹⁸

Electrophysiology and Arrhythmias

Sex is an important determinant of ion channel and transporter expression,¹⁹ as well as of electrophysiologic properties and arrhythmia occurrence.²⁰ With the use of a US national database on cardiac device implantations, Mohamed et al. show that women are at greater overall risk of implantation-related adverse effects, although certain specific complications (such as infection) were more common in men.²¹ Based on these findings, Humphries and Hawkins conclude that implanters need to review their technique and develop optimized approaches to avoid sex-specific mechanical complications.²²

Devaux et al. examine sex-related differences in vasovagal syncope, based on data obtained in 2 randomized multicentre placebo-controlled drug trials, Prevention of Syncope Trials I and II.²³ They find systematic sex-dependent differences in age at presentation (women are younger), baseline blood pressure (lower in women), symptoms (more feelings of heat, seizures, and postevent fatigue in women), and recurrence rate (higher in women). They suggest that recognition of these differences in clinical presentation may help in diagnosis and therapeutic decision making.

Vascular Disease

Noticeably lacking from the articles in this issue are papers regarding sex-related vascular complications. It is well known that women have different pathophysiology, presentation, and outcomes of coronary artery disease compared with men.²⁴ The specificity of vascular disease manifestations in women

is not limited to coronary artery disease: Women present particular features of vascular aneurysm pathophysiology and outcomes,²⁵ as well as of peripheral vascular disease.²⁶ Self-management approaches are an interesting and effective technique in the management of cardiac pain in women.²⁷

The Future

The papers in this focus issue attest to the increasing attention and knowledge base regarding sex-specific cardiovascular disease outcome predictors, but much more work needs to be done before we can generate detailed sex-specific management guidelines. Necessary first steps include sex-specific reporting of results with prespecified subgroup analyses by sex and adequate statistical power to provide definitive results in both sexes. Nevertheless, it is important to recognize the great progress being made while being attentive to the major areas in which much more work is needed.^{28,29}

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