

Sex-specific issues related to cardiovascular disease: a synopsis of the 2007 supplement

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Accompanying this issue of *CMAJ* is a special supplement entitled “A comprehensive view of sex-specific issues related to cardiovascular disease” (available online at www.cmaj.ca/cgi/content/full/176/6/S1).¹ The supplement was prepared by myself and other members of the GENESIS (Gender and Sex Determinants of Cardiovascular Disease: from Bench to Beyond) team, comprising over 40 multidisciplinary scientists across Canada who are studying the sex and gender determinants of cardiovascular disease. GENESIS is an interdisciplinary capacity enhancement team that receives funding from the Canadian Institutes of Health Research and the Heart and Stroke Foundation of Canada (www.genesisteam.ca). In this commentary, I highlight some of the findings reported in the supplement.

The GENESIS team has summarized the current knowledge of sex and gender determinants in cardiovascular disease following a comprehensive review and evaluation of peer-reviewed literature from the MEDLINE, EMBASE, Cinahl and Cochrane databases and literature from the Web sites of the World Health Organization, the American Heart Association, the British Heart Foundation, the Canadian Institute for Health Information, the US National Center for Health Statistics, the US Food and Drug Administration and the US Centers for Disease Control and Prevention. Eight broad topics addressed in the supplement (Box 1) were derived from the mandate of the GENESIS team to examine the sex and gender determinants of cardiovascular disease from bench to bedside, where “sex” represents biological and genetic factors, and “gender” represents behavioural and environmental factors. Through this comprehensive review, we have sought to provide a general overview of the importance and contributions of sex and gender to the development, manifestation, management and outcomes of cardiovascular disease. We have also identified key knowledge gaps to help guide research in the near future to gain a better understanding of why cardiovascular disease affects women and men differently (Box 2).

The literature review revealed major sex-specific differences in the burden of cardiovascular disease, the prevalence of risk factors, the presentation of disease, and the optimal diagnostic and therapeutic strategies for the management of patients. However, the reasons for these differences are less clear. For instance, why are young women with acute coronary syndrome at greater risk of death than young men with acute coronary syndrome are, and why is the risk of death from cardiovascular disease significantly greater among women with diabetes than among men with

diabetes? Similarly, why is the risk of stroke greater among women with atrial fibrillation than among men with atrial fibrillation, and why do women present with different symptoms of acute coronary syndrome than do men?

Although the bulk of knowledge about cardiovascular disease comes from studies involving adults, our review of risk factors in girls and boys highlights the increasing prevalence of these conditions among our youth. Research into risk factors for cardiovascular disease in young populations carries a great potential for elucidating the sex- and gender-specific differences observed in adulthood and may help to identify targeted interventions at an early age. Even at the genetic level, few studies have focused exclusively on women or have examined men and women separately. Our review of genetic determinants of hypertension has revealed that genes (even aside from the sex chromosomes) show variation in their expression and action in women and men. A better understanding of the pathogenetic mechanisms of sexual dimorphism in the development of cardiovascular disease is clearly needed.

Historically, women have been underrepresented in clinical trials investigating issues related to cardiovascular disease. The lack of good trial evidence and sex-specific outcomes has led to assumptions about treatment in women that may or may not be correct. These knowledge gaps may also explain why cardiovascular health in women is not improving as fast as it is in men. Over the past few decades, rates of death from cardiovascular disease have steadily declined among men, whereas they have remained stable among

Box 1: Topics addressed in the supplement*

- Burden of cardiovascular disease in women and men
- Cardiovascular risk factors in girls and boys
- Cardiovascular risk factors in women and men
- Differences in cardiovascular presentation in women and men
- Genetic and sex determinants of hypertension and cardiovascular disease
- Delivery of cardiac care in women and men
- Outcomes of cardiovascular disease in women and men – clinical trials
- Outcomes of cardiovascular disease in women and men –post-admission drug therapy

*The supplement is available online at www.cmaj.ca/cgi/content/full/176/6/S1.

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women. It is also becoming increasingly evident that gender-specific differences in behavioural as well as cultural, psychosocial and socioeconomic status are responsible, to various degrees, for the observed differences in outcomes of cardiovascular disease between women and men. However, the interaction between such sex- and gender-related factors and outcomes of cardiovascular disease remains unknown for the most part. Thus, although a large body of knowledge about cardiovascular disease has now accumulated, a comparatively small amount of this knowledge has focused on women. For this reason, substantial knowledge gaps exist in the literature.

Interest in the sex and gender determinants of cardiovascular disease is growing rapidly. Since the submission of the *CMAJ* supplement, several pivotal studies have been published.²⁻⁴ In March 2006 the *Journal of the American*

Box 2: Key knowledge gaps in the understanding of why cardiovascular disease affects women and men differently*

- Why are the incidence and mortality of cardiovascular disease decreasing among men but stable among women?
- Why are young women with acute coronary syndrome at greater risk of death than young men with acute coronary syndrome?
- What is the relative importance of genetic, biological and environmental risk factors for cardiovascular disease in girls and boys and their persistence into adulthood?
- What are effective prevention and treatment strategies for obesity in girls and boys?
- Why are women with diabetes at significantly greater risk of death from cardiovascular disease than men with diabetes?
- Why do women present with different symptoms of acute coronary syndromes than do men?
- What are the pathogenetic mechanisms of sexual dimorphism in the development of cardiovascular disease?
- Are age, comorbidities, clinical presentation, ethnic background and socioeconomic status important determinants of access to care for women?
- What strategies can be used to optimize the detection and treatment of cardiovascular disease among women?
- What is the biological and pathophysiological basis for less extensive angiographic disease in women?
- Why is the effectiveness of primary and secondary prevention different between women and men?
- Are cardiovascular drugs as effective in women as in men?
- What therapies can be developed that are tailored to sex and gender?
- What are the interactions between sex- and gender-specific factors and cardiovascular disease outcomes?

*A more extensive list of knowledge gaps can be found in the supplement¹ (available online at www.cmaj.ca/cgi/content/full/176/6/S1).

Medical Association published a special issue devoted to women's health (*JAMA* 2006;295[12]:1339-474). Of the 6 original contributions, 4 specifically focused on cardiovascular disease. In addition, members of the GENESIS team published several important studies after the supplement was written. For example, Karp and colleagues⁵ demonstrated that the magnitude of mortality reduction after an acute myocardial infarction was smaller among women receiving statin therapy than among men receiving statin therapy. Using a longitudinal adolescent cohort, Dasgupta and colleagues⁶ reported that boys were more likely than girls to have high systolic blood pressure as they approached adulthood. Guru and colleagues⁷ reported that, although women were more likely than men to be readmitted to hospital with unstable angina and heart failure after coronary artery bypass graft surgery, they experienced similar survival outcomes.

If the knowledge gaps around sex and gender determinants of cardiovascular disease are to be addressed appropriately, it is imperative that well-designed, large-scale studies be conducted in which women are adequately represented. Because previous studies overwhelmingly involved men, there are relatively few data available to guide diagnostic and therapeutic strategies for cardiovascular disease in women. Thus, future studies must be sufficiently powered to allow statistical inferences and identification of sex-specific outcomes.^{8,9} Canadian granting agencies should consider issuing explicit policy statements about the need for representative inclusion of both sexes in submitted studies.

The data presented in the *CMAJ* supplement establish that there are many important sex- and gender-specific differences in cardiovascular disease. Much remains to be done to optimize the management of cardiovascular disease in women and thus help prevent a disease that is the leading cause of death among women.

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Competing interests: None declared.

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Women and cardiovascular disease

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Cardiovascular disease is responsible for half of all deaths among women aged 50 and older in Canada and the United States. Nevertheless, women have less heart disease than men. Perhaps this is the main reason why the study of heart disease in women is a relatively recent phenomenon. In the last few years interest has increased (in parallel with increasing numbers of female scientists), evidenced by the recent publication of at least 3 books on the subject of cardiovascular disease in women.^{1–3} This increased interest appears to have prompted the timely publication of the *CMAJ* supplement “A comprehensive view of sex-specific issues related to cardiovascular disease” (available online at www.cmaj.ca/cgi/content/full/176/6/S1).⁴ The 480 mainly recent references cited in the supplement are further evidence of the increased interest in this area. In addition to highlighting the relevance of this issue, the reviews contained in the supplement illustrate the many information gaps facing health care professionals and decision-makers. In this commentary, I have taken the liberty of highlighting some of

the deficiencies in the literature, through the critical appraisal of key articles cited in the supplement, as well as some deficiencies in the review itself.

After many years of studies restricted to men or without sex-specific analyses, there are surprisingly few original sex-specific studies in the same cohort. For the first paper in the *CMAJ* supplement, “Burden of cardiovascular disease in women and men” (page S1), Rabi and Cox performed a systematic review of published cohort, case-control or case-cohort studies of prevalence, incidence and mortality related to cardiovascular disease, atrial fibrillation and congestive heart failure in women and men.⁴ It is notable that only 33 original articles were found that presented data on any of these outcomes in both sexes.

Many papers have been written about the decline in cardiovascular disease among men but not among women over several decades, with the inference that men receive more preventive and therapeutic medicine. In their systematic review, Rabi and Cox cite 3 different papers reporting cardiovascular

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