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Invited commentary

Sex matters to the heart: A special issue dedicated to the impact of sex related differences of cardiovascular diseases

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Ever since the early 1980s most cardiovascular research has focused on men [1]. This phenomenon has led to the under appreciation of sex-differences in cardiovascular disease (CVD) from an etiological, prognostic, diagnostic and therapeutic perspective. Several initiatives to promote women's health, such as the Women's Health Initiative [2] have been initiated and have changed the practice of cardiovascular disease prevention in women over the past decade. This ultimately led to the first guidelines for cardiovascular disease prevention in women by the American Heart Association in 1999 [3]. These initiatives have increased the awareness that medical practice in cardiovascular disease may differ between men and women and that the 'one size fits all' approach may not hold. This special issue of the journal is dedicated to sex-differences in CVD risk factors, presentation, underlying mechanisms, treatment and cross-links with other diseases such as autoimmune diseases.

One of the factors that may worsen outcome in women as compared to men is the perception of cardiovascular risk and the decision to seek medical care when experiencing complaints [4]. Research shows that more than half of the women would still be hesitant to call the emergency number when thinking they are experiencing a myocardial infarction. Several studies report that time from symptoms to first medical contact as well as time from hospital arrival to reperfusion is significantly longer in women as compared to men [5]. The reported median delays are between 15 min to more than an hour in women. This fact underscores the need for campaigns educating women and the primary care system about the importance of recognizing a-specific symptoms in order to improve survival.

Indeed, in the last decade intensive public efforts to educate women about their risk of heart disease have been quite successful as a recent survey showed that awareness of heart disease among women nearly doubled in 10 years [6]. Given the positive correlation between awareness and cardiovascular disease risk reductions in women, it is important that the emphasis on these campaigns remains high.

Among sex differences in clinical presentation of CVD, more women than men present with acute coronary syndromes but non-obstructed arteries [7]. The review of F. Crea and coworkers in this issue of Atherosclerosis summarizes the clinical presentation of CVD in men and women, and underscores the sex-differences in underlying pathology. Cardiac ischemia due to coronary microvascular obstruction is more prevalent in women as compared to

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men, gives rise to chest pain in women, and is subject to underdiagnosis. In addition, increasing evidence points towards coronary microvascular endothelial inflammation as cause for heart failure with preserved ejection fraction (HFpEF) [8], a condition that affects women more than men. Similarly to coronary microvascular obstruction, HFpEF is also subject to under-diagnosis due to the lack of biomarkers that are implicated in the disease process. The Dutch Queen of Hearts consortium aims to discover and validate new biomarkers related to microvascular endothelial inflammation to improve the diagnosis of HFpEF [9].

Next to differences in the microvasculature, also differences in the pathological substrate of macrovascular obstruction are quite prominent between men and women. This is reviewed by Yahagi [10] and coworkers who summarize pathological observations that are considered as the underlying substrate for CVD. Women have more stable plaques, and more plaque erosion as underlying cause for sudden cardiac death as compared to men in whom more vulnerable plaques and more plaque rupture are reported under similar conditions [11,12]. This is supported by research from our group showing that women undergoing carotid endarterectomy have more stable plaques as compared to men. Moreover, the predictive value of plaque haemorrhage as predictor for secondary outcome was conveyed to men [12,13]. In the review of Yahagi [10], the role of smoking and the menopause is being discussed as factors that could be causally related with accelerated CVD in women. It has been suggested that sex hormone status explains the differences between men and women and their progression to CVD. Indeed, estrogens in women appear to protect against CVD as loss of estrogens during and after menopause goes hand in hand with an increased cardiovascular risk. However, whether hormone replacement therapy after menopause confers cardiovascular benefit or harm remains controversial and appears to depend on time since menopause at the initiation of hormone replacement therapy.

Women have specific risk factors for CVD that are related to pregnancy disorders such as gestational diabetes, hypertension and preeclampsia as well as endocrine changes in women of reproductive age such as early menopause. These risk factors are reviewed by Appelman [14] and coworkers who also compare risk factors for CVD between men and women. The risk factor that appears to be most sex-specific for CVD is prolonged smoking which appears to be more harmful for women than for men.

Fig. 1 provides a schematic overview.

An explanation for sex differences apart from hormones comes from Winham [15] and coworkers who discuss the role of genetics and sex chromosomes in particular. Sex chromosomes are beginning to be recognized as important players in sex differences in disease development, independent of sex hormones [16]. The human X and Y chromosomes evolved from a pair of autosomes over the past 160 million years. The sex chromosomes differentially evolved into a relatively large, gene-rich X chromosome and a small, gene-poor Y chromosome. Only 3% of ancestral genes survived on the human Y chromosome compared to 98% on the X chromosome. It was recently discovered that the genes conserved on Y that are expressed in cells and tissue types throughout the body are involved in decoding and interpreting the entirety of the genome [17]. The Y chromosome is present exclusively in men and contains the sex-determining region, the primary determinant of testicular development, spermatogenesis and masculinization. The Y chromosome has mostly been excluded from the larger genome-wide association studies (GWAS), due to technical difficulties and also due to the thought that the Y chromosome could be considered as genetic wasteland [18]. Just recently this idea was contradicted as many Y chromosomal genes were found to be haploinsufficient regulatory genes [17], and the SNPs (single-nucleotide

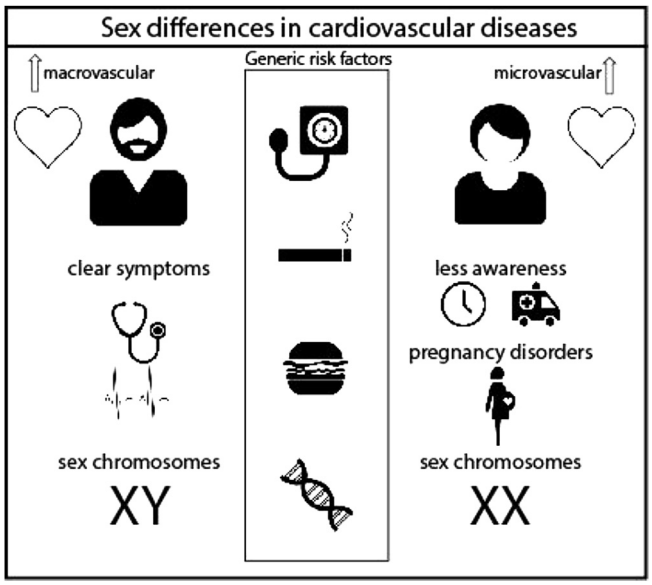

Fig. 1. Schematic overview of sex differences in cardiovascular disease. Although risk factors for CVD overlap between sexes, some sex-specific risk factors have been identified such as pregnancy disorders, awareness of being at risk for CVD and the regulatory role of sex chromosomes.

polymorphisms) on the Y chromosome were associated with CVD risk factors such as blood pressure [19]. In addition, inheritance of coronary artery disease in men was associated with a specific haplotype on the Y chromosome [20], independent of sex hormones and aggression.

Also, the X chromosome has only been included in 33% of the analysis from all GWAS from 2010 to 2011 [21], This underrepresentation of X in GWAS is particularly striking in the context of significant (≈5%) contribution of X chromosome to the overall content of the human protein-coding genome. Regulation of the X chromosome is especially of interest in diseases that have a different prevalence between sexes. Inactivation of the X chromosome in women entails the random silencing of one of the two X chromosomes to compensate for the fact that men have only one, so called dosage compensation. The mechanism of X chromosome inactivation is however incomplete and flexible so it regulates gene expression between sexes, individuals and tissues [22]. The X chromosomes contain information involved in inflammation, and contribute largely to autoimmune diseases that are highly female-specific. Biological targets for X-linked miRNAs are amongst others FOXP3, CTLA-4, PDCD1 and members of the CBL and SOCS ubiquitin family, all related to inflammation and endothelial function [23]. Indeed it has been suggested that X-chromosome-genomic context affects X-located miRNAs thereby contributing to the enhanced immune response in women [24]. X chromosome instability (loss of the second X) in peripheral blood cells is directly linked to the development of female specific autoimmune diseases and cardiovascular diseases [25,26].

Autoimmune diseases have a high prevalence in women and also associate with cardiovascular disease risk. In autoimmune diseases the immune response to self-antigens results in damage or dysfunction of tissues. They can occur systemic or can affect specific organs or body systems. For most autoimmune diseases there is a clear sex difference in prevalence. In autoimmune disorders such as Addison's disease, scleroderma, systemic lupus erythematosus (SLE), Sjorgen's syndrome, and thyroiditis, females represent >85% of cases whereas myocarditis appears to be male-specific [27]. The microvasculature in women may play an important role in the

predisposition of women with autoimmune diseases to develop accelerated CVD as reviewed by Gianturco and coworkers in this issue [28].

In summary, there are profound sex-differences in heart disease. This issue of Atherosclerosis is dedicated to this timely topic which is increasingly being acknowledged. Further research initiatives with the objective to personalize cardiovascular care for men and women are eagerly awaited.

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