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EDITORIAL

Universality of sex differences in cardiovascular outcomes: where do we go from here?

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This editorial refers to 'The association of long-term outcome and biological sex in patients with acute heart failure from different geographic regions', by J. Motiejuanaite *et al.*, on page 1357.

The bodies of females and males differ at the most fundamental genetic level due to the presence of the sex chromosomes. The genes on these chromosomes not only direct development of the reproductive organs with subsequent production of sex steroid hormones, but also influence development of other organs and expression of genes on the autosomes.[1–3] These genetic and hormonal differences between females and males allow for the female cardiovascular system to adapt to changes necessary to sustain a viable foetus, including increases in blood volume, autonomic regulation of blood pressure, and cardiac dynamics, i.e. general cardiovascular function. Given these basic genetic and hormonal influences on all cells of the cardiovascular system including vascular endothelium, vascular smooth muscle, adventitial cells, cardiac myocytes, and adrenergic and parasympathetic nerves (indeed, 'every cell has a sex'[4]), should we not expect to find sex differences in incidence, prevalence, morbidity, and mortality in cardiovascular disease between females and males?

Sufficient evidence points to sex differences in cardiovascular disease associated with autonomic function (i.e. arrhythmias, Raynaud's disease, menopausal hot flushes, hypertension, hypertension of pregnancy, and pulmonary hypertension), vascular remodelling associated with atherosclerosis, or spontaneous coronary artery dissection and heart failure.[5–10] Using data from global databases/registries and clinical trials, the recently published study by Motiejuanaite *et al.*[11] further substantiates sex differences (by self-report as a man or woman) in biological parameters associated with hospital admissions for acute heart failure. The international GREAT registry that included patients from Finland, France, Italy, Spain, Switzerland, Czech Republic, Lithuania, the USA, Canada, China, Japan, and South Korea identified physiological differences at admission between men and women including age, body mass index, systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate, obstructive pulmonary disease, acute coronary syndrome, and acute arrhythmias. This cohort was compared with the OPTIMIZE-HF study cohort[12] from the USA for validations, and the REALITY-AHF (Japan)[13] and ASIAN-HF (India and Singapore)[9] studies. The differences between males and females in patient baseline characteristics persisted throughout the geographical regions.

The authors then went on to evaluate 1-year mortality. This analysis included culturally driven aspects of medical care including use of evidence-based treatment. The median hospital stay for men was longer than for women, and women were less often prescribed what is considered optimal therapy for heart failure that consists of a combination of a beta-blocker and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and aldosterone receptor antagonist. In spite of this difference in prescribing practice, women had lower 1-year mortality than men when the data were adjusted for age and other covariates that differed at baseline. However, the long-term outcome differed by geographical region, with woman from Northeastern Asia having lower 1-year mortality compared with those from Western and Central Europe or North America. The reasons for these regional disparities in outcomes for women are unclear, but most probably reflect the intersection of genetic variants associated with some risk factors for development of cardiovascular disease with the influence of cultural and environmental factors such as socioeconomic status, lifestyle including diet and activity, access to care, etc.

Although the authors identify several limitations of their study including the self-report of sex status as gender and incomplete or missing data related to some parameters including the history of heart failure, the major observations of sex differences in clinical presentation and 1-year survival outcomes for acute heart failure are validated globally. This outcome is to be expected given the universality of basic sex differences at the genetic and hormonal levels. The

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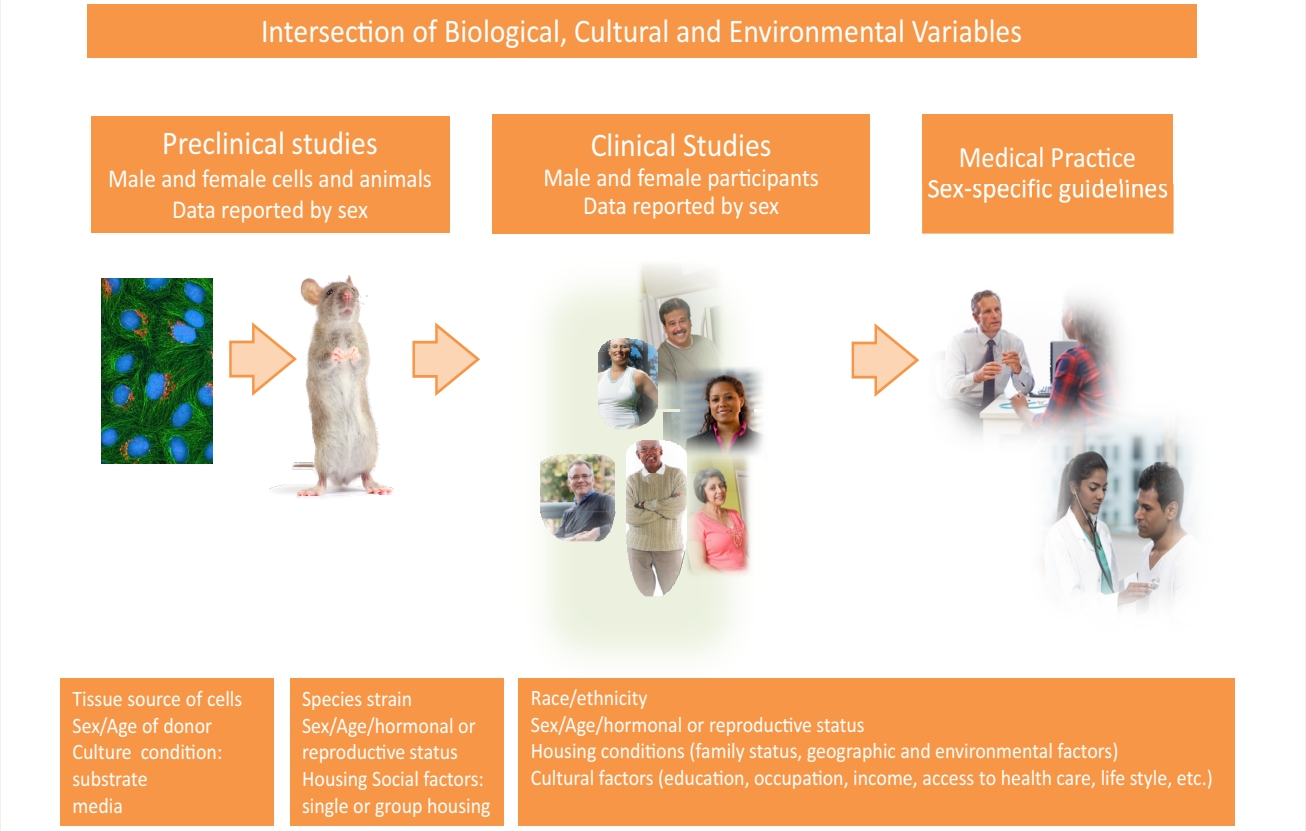

Figure 1 Schematic depicting the next steps needed to transform how evidence is obtained and applied for an individualized approach to clinical care for men and women. The process starts with preclinical studies that utilize cells from male and female donors, animal studies that include both male and female animals, and clinical studies that include male and female participants. An important component of transforming the evidence is to require reporting of data by sex, including both clinical and cultural parameters that encompass gender; even if the study was not powered to detect sex differences, having transparency for the data allows for hypothesis development, new study design, and combination of data by sex for meta-analyses.

main question remains what to do with this information. That is, where do we go from here?

The next steps are clear. Basic understanding of how genetic sex and hormonal factors influence cellular processes associated with development of cardiovascular disease, and in this particular case, heart failure, needs further investigation. This information should be used to develop new therapeutic approaches. While 'optimal therapies' are recommended in clinical practice guidelines, these were often not developed by understanding how age differences in sex hormones, decreases of oestrogen in women, but sustained levels of testosterone in men, affect the therapeutic targets, i.e. enzyme activity, receptor expression, or binding efficacy. Many of these therapeutic approaches were developed with a singular approach to heart failure while there is now a differentiation of heart failure with and without reduced ejection fraction. Although women may have been included in the clinical studies, data were not reported by sex or gender; therefore, it remains unclear which therapies might be optimal for men or women with or without preserved ejection fraction. The scientific and clinical communities have the responsibility to account for sex as a biological variable and to understand that hormonal status changes throughout life. These variables should be taken into account in design of basic science studies into the mechanisms of disease as well as in development of novel therapeutics. Data should be reported by sex so as to clarify where sex differences might be considered critical to future diagnosis and treatment. Editorial boards have a responsibility to ensure that the reporting of the data is transparent. Available data on sex differences as reported by Motiejunaite *et al.* should be implemented into clinical practice. For example, if women present at older age than men for heart failure, when should monitoring be initiated to optimize prevention, diagnosis, and treatment? The intersection of cultural and environmental factors that influence gender norms, identity, and relationships need to be broadened and considered in influencing global and regional disparities in disease and outcomes.

The study by Motiejunaite *et al.* provides us with the motivation to begin to examine more closely the why of sex differences[14,15] in disease manifestation and outcomes, and to translate those new findings into improving patient care (*Figure 1*).

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