Cardiovascular risk assessment: more sex please

Dr Julie George PhD
Farr Institute of Health Informatics Research
University College, London

Treatment of individuals at higher risk of cardiovascular events with primary prevention medication has been an important part of coronary care for over 20 years. During this time, substantial gains have been made in reducing mortality from coronary heart disease (CHD),(1) in part due to use of primary prevention medications such as statins.(2) Yet, at all ages, these gains in mortality reduction have not been shared equally between men and women.(3,4) While the causes of these age and sex differences in mortality reductions are not well understood, it is recognised that cardiovascular risk estimates by primary care physicians are often imprecise, contributing to suboptimal preventive treatment in real-world clinical practice.(5) There is a need for more accurate sex-specific risk assessment, based on better understanding of sex differences in the way circulating biomarkers affect cardiovascular outcomes, in order to drive further reductions in cardiovascular disease (CVD) mortality.

Dr Gohar and colleagues have undertaken a substantial systematic review of the evidence for sex differences in baseline levels of established and emerging plasma-based biomarkers and their associations with cardiovascular outcomes.(6) Some biomarkers, such as Lp(A) and LDL-C, have been the subject of multiple studies the results of which often contradict each other while other studies have shown greater consistency about the associations between raised biomarker levels and associations with cardiovascular disease in men or women. The importance of understanding the nuances of risk associated with differing levels of circulating biomarkers is demonstrated by lipid studies in which women consistently have higher concentrations of HDL cholesterol but the same association with CVD endpoints compared with men, while baseline levels of LDL cholesterol were similar for both sexes but the strength of association with CVD endpoints varied, one study favouring men and another favouring women.

Evaluating the meaningfulness of these results is further complicated by studies included in the review a) being of variable quality, b) coming from different periods in recent cardiovascular history, c) including different age groups and examining different CVD outcomes. Gohar et al successfully identify the association of risk factors with specific CVD endpoints - they included a range of outcomes including coronary heart disease (CHD), heart failure, atrial fibrillation and stroke as well as composite outcomes – the authors do not provide any comparisons of how endpoints are measured or discuss how differences in outcome definitions might help in understanding conflicting findings. Nor have all outcomes been subject to the same sex-specific analysis and like a previous review far more studies have focussed on sex differences in coronary heart disease than in stroke.(7)

In what is perhaps a greater service to understanding in this area, Gohar et al. have also documented the paucity of studies that have presented sex-specific results. The authors identified 360 papers on the association between selected biomarkers and CVD outcomes in healthy populations. Out of

these, 171 were single sex studies. A further 134 did not report sex-specific results, leaving a total of 55 papers with direct comparisons between men and women. The authors point out that both men and women were well represented in the studies included in the review, offering multiple opportunities for sex-specific analyses which were not taken. Particularly disappointing, as the authors point out, is that with emerging biomarkers there are no studies reporting sex-specific results, despite earlier animal studies indicating significant differences by sex. The lost opportunity from 85% of the studies in this area not providing relevant analyses to help understand the underlying aetiology of cardiovascular disease suggests the need for more organised action by the scientific community to ensure this happens in future.

The United States has led the way with taking organised action to ensure better understanding of differences between men and women in the development of disease with the National Institutes for Health (NIH) Revitalisation Act in 1973 requiring inclusion of women in all NIH-funded clinical research, followed in 2014 by a requirement for gender balance in all cell and animal studies.(8) The European Commission has more recently joined the fray with an explicit requirement for gender equality in research, including required integration of **"…** the gender dimension in the content of Research and Innovation".(9) The newly published Lancet Commission on Women and Health has called for research funding agencies to mandate that research studies enrol women and make sex differences a core component of research, and more specifically that "basic, clinical, social science and public health research projects disaggregate study populations by sex and explicitly consider gender in their design, implementation, analysis and reporting".(10)

One of the difficulties of such requirements is the need for larger sample sizes with sufficient power to allow disaggregated analyses. NIH is addressing this point by supporting existing grant holders with additional funding to recruit additional subjects. Electronic health records provide an alternative means of generating large cohorts for outcomes research but although well powered for comparative analyses by gender their application for studying emerging biomarkers is more limited.(11–13)

So does investment in sex-specific analyses make a useful difference to the accuracy of risk prediction? Answers are difficult but it is instructive to reflect on the evolution of the American Heart Association's guideline on the prevention of coronary heart disease in women. First published as a consensus panel statement in 1999 with limited references,(14) it has now evolved into an effectiveness-based guideline with six times as many references as sex-specific data on risk factors for coronary heart disease have accumulated.(15) With greater consistency in publishing sex-specific analyses, the evolution of our understanding of cardiovascular risk in men and women will continue to develop.

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