AFFAIRS OF THE HEART:

OUTCOMES IN MEN AND WOMEN WITH HYPERTROPHIC CARDIOMYOPATHY

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Variations in clinical outcomes between men and women with cardiovascular disease have been extensively investigated and reported. In some relatively uncommon disorders such as Takotsubo syndrome and spontaneous coronary artery dissection there is a clear female predisposition. There are also differences between men and women with more frequent cardiac conditions such as coronary artery disease and aortic stenosis.[1]

A consistent observation in studies of hypertrophic cardiomyopathy (HCM) is a male predominance of around 60%.[2-4] In individuals with mild LV hypertrophy, women may be under represented due to diagnostic bias since they tend to have less hypertrophy and fewer electrocardiographic abnormalities. [2,5] However, the male predominance persists throughout the range of left ventricular hypertrophy and is accentuated at the severe end of the spectrum.[6] This suggests that additional factors linked to the sex of individual patients play a role in clinical penetrance and expression of this primarily autosomal dominant disease. For example, the hearts of men with HCM tend to have more fibrosis on histological examination than their female counterparts [7] but paradoxically females more frequently develop heart failure symptoms.[2 8] Men also experience more exercise induced ventricular arrhythmias (a rare event in both sexes)[9] but there are conflicting data about the effect of sex on the prevalence of left ventricular outflow tract obstruction, with some studies reporting a higher prevalence in males and *vice versa*.[2,4,8,10]

The biological explanation for these sex differences in HCM remains the subject of speculation. In a transgenic mouse model of an α-myosin heavy chain mutation, mice of both sexes developed similar degrees of hypertrophy in early life, but at 10 months, male mice exhibited more aggressive disease with the development of LV dilation and systolic

impairment, whilst female mice maintained LVH with preservation of systolic function.[11] Other experiments have suggested sex specific responses to pathological stimuli such as adrenergic stimulation. In humans, genetic variation in the androgen receptor has been suggested as a possible contributor to sex related differences in clinical phenotype.[12]

In this issue of the Journal, Geske and colleagues[13] describe the influence of sex on all cause survival in a large cohort of patients evaluated at a single centre in the US. They show that women have higher all cause mortality than men and conclude that a more aggressive therapeutic approach may be needed in women, although the nature of this is not elaborated.

There are relatively few studies with a specific focus on the association between sex and clinical outcomes in HCM, although sex is considered as a covariable in many outcome studies. Indeed, similar findings with respect to all cause mortality have been reported recently in a Chinese population.[8] Geske and colleagues compare their findings to a 2005 study of around 900 patients in which there was an association between female sex and the combined end point of symptomatic progression or death from heart failure or stroke, but not with all cause mortality.[2] There are, of course, many possible explanations for this disparity, some more prosaic than others. Geske et al suggest that sample size may be the cause but other methodological considerations include the exclusion of ICD shocks from their analysis–which in contemporary studies contribute up to 20-25% of SCD end-points–and referral bias (more than 25% of their patients underwent invasive septal reduction therapies).

If we accept–for sake of argument–that females with HCM do have a higher all-cause mortality than men, we need to better understand the cause as without this knowledge the issue is difficult to address. Studies in patients with coronary artery disease have shown that confounders such as age and comorbidities partly explain differences in outcome.[1] There is some suggestion that this may be the case in the study by Geske and colleagues as women were older than men and thus may have been exposed to a higher burden of co-morbidities. As in other settings, it is also important to consider non-biological explanations. For example, women with acute coronary syndromes are less likely to undergo cardiac catheterization and have longer reperfusion delays than men.[1] Women with cardiovascular disease are also less likely to be prescribed statins, renin angiotensin blockers and β-blockers.[1] These differences are unlikely to represent a conscious denial of therapy but may represent a failure to recognise symptoms in women with cardiovascular disease. Disparity in cardiovascular outcomes in women may also be driven by socioeconomic and psychosocial factors. For example, compared to men, women are more likely to live in poverty and have higher rates of depression.[14] It is also possible that women benefit less from established therapies.

Improved understanding of the epidemiology of HCM and its relation to non medical factors that may influence outcomes is clearly necessary. A major message, however, is that there needs to be much greater emphasis on personalised medicine in HCM, based on an individualised approach to diagnosis and risk assessment.

Conflicts of interest:

The authors have no conflicts of interest to declare.

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