Invited Editorial

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Female Sex and Persistent Inequalities in the Care of Patients with Hypertrophic Obstructive Cardiomyopathy: A Call to Action

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According to the ancient Indian scripture, the Bhagavad Gita

"Everyone is equal to the wise one"

Inequalities in healthcare have existed for decades and have been exemplified by the COVID-19 pandemic. Specific characteristics such as sex, ethnicity, age and disability, social, cultural and economic factors, and geography have all been implicated. Cardiovascular disease (CVD) has historically been viewed as a "*man's disease*". Although campaigns have helped to increase awareness, CVD in females remains understudied, under-recognised, underdiagnosed, and undertreated.[1] While biological differences between females and males likely contribute to differences in outcomes, disparities in preventive strategies, diagnosis and appropriate treatment also play a role. Scientific societies and the World Health Organisation (WHO), recognise the complex interplay between sex and gender as important factors, in addition to the biological science, which when addressed holistically, may reduce the burden of CVD.[1–3]

Similar to other cardiovascular diseases, sex related differences have been reported in hypertrophic cardiomyopathy (HCM). Olivotto et al.[4] studied 969 consecutive HCM patients in Italy and North America, with a follow up period over 6.1±6.1 years. The authors reported that at initial evaluation in a tertiary referral setting, female patients were older (47±23 vs. 38±18 years; p<0.001), more likely to exhibit left ventricular outflow tract obstruction and in a worse New York Heart Association (NYHA) functional class. Although HCM related mortality was similar between sexes, females were more likely to progress to NYHA functional class III/IV and had higher mortality due to heart failure and stroke. A recent meta-analysis on sex-related differences in HCM with a total of 9,427 patients, including 3,719 females, reported that females were at increased risk of all-cause mortality (OR:1.63, 95% CI:1.26–2.10, p≤0.001),

HCM-related mortality (OR:1.47, 95% CI:1.08–2.01, p=0.015), and worsening HF or HF hospitalization (OR:2.05, 95% CI:1.76–2.39, p≤0.001).[5]

In this issue, Javidgonbadi et al[6] performed a retrospective analysis of a non-selected cohort of patients with obstructive HCM (oHCM) to identify factors that account for excess mortality in female patients. The authors interrogated databases in all ten hospitals in the West Götaland Region in Sweden which yielded 250 patients with oHCM, 123 (49%) females. Clinical information was systematically recorded at baseline and last assessment. To facilitate comparison on the effect of therapy, the authors converted beta-blocker doses to an equivalent dose of metoprolol. For survival analysis, the cohort was further divided into 83 pairs matched for age at diagnosis, degree of LVH, LVOT gradient and treatment strategy (medical therapy only, pacing, or myectomy). The authors should be commended on collecting follow up data for the entire cohort for a mean of 18.1 years.

There are three pertinent findings from this study. Firstly, females were on average 11 years older than males at the time of diagnosis with oHCM and had a more severe disease phenotype, as evident by greater BSA adjusted left ventricular septal hypertrophy and greater proportion with severe symptoms, NYHA class-III. These findings are consistent with previous studies. Unlike ischaemic heart disease where biological factors may explain clinical expression of the disease at a later stage in females, more plausible reasons in oHCM include delayed recognition, reluctance of females to seek medical attention until symptoms are severe and physician bias. It is well established that females exhibit 1-2mm lower absolute wall thickness to males.[7] The lack of sex-specific diagnostic criteria in HCM and the widespread use of absolute wall thickness in clinical practice, means that females need to exhibit proportionally greater wall thickness than males to satisfy a diagnosis of HCM.

Females with CVD may present at a later stage due to a combination of false perceptions, atypical symptoms but also social, cultural, and economic barriers. Physicians may misinterpret symptoms in females and evidence suggests that even guideline recommended investigations may be delayed or performed less frequently in females.[8] This notion is further reinforced in the study by Javidgonbadi et al,[6] where 51% of males underwent genetic testing compared to only 28% of females, despite the fact that HCM is largely inherited in an autosomal dominant pattern and genetic testing in an affected individual has an integral role in familial cascade screening.

Secondly, females had excess disease-related mortality compared to males (2.8% versus 1.4% per annum). The excess female mortality stemmed from the older age groups (≥50 years) and was due to heart failure and myocardial infarction related deaths. Although at first glance excess female mortality may be attributed to delayed diagnosis and treatment and worse clinical profile at baseline compared to males, the mortality differences persisted even in groups matched for age and established risk factors, such as LVOT gradient and NYHA class at diagnosis. Most studies in the literature demonstrate excess female morbidity and mortality, with some reporting higher all-cause mortality among female patients, while other studies showing an excess of female death from heart failure or stroke but no difference in overall mortality. In a large multicenter report of 4893 patients (36.1% females) with HCM presenting at 7 European referral centers, the investigators found excess mortality in females compared with males that persisted throughout the age spectrum.[9] Such findings suggest that biological factors and postmenopausal endocrine changes may impact the clinical course of females with HCM, although accrued myocardial injury and resultant fibrosis due to delayed recognition and

treatment is also plausible. Unfortunately, the study by Javidgonbadi et al [6] did not include data from cardiovascular magnetic resonance imaging.

Finally, from a therapeutic perspective higher beta-blocker dose, above the cohort-median, was associated with reduced disease-related mortality, irrespective of sex, with survival curves separating 5 years after diagnosis. Betablocker therapy was well tolerated as more than 85% of the cohort were established on treatment at follow-up and only 3.2% discontinued treatment during the course of the study. However, fewer females received betablocker therapy after diagnosis (64%) compared to males (78%) and in smaller doses, which is surprising considering females were more symptomatic and with similar prevalence of LVOT obstruction at diagnosis. Female patients were prescribed more frequently calcium channel antagonists which in this study was associated with increased disease-related mortality. The reason for the different prescribing approach was unclear and could not be justified based on the clinical information available.

By nature of the study design and cohort size, these results should be viewed with caution. Further research in the form of prospective randomised trials is required to evaluate disease-modifying effects of drug therapy. In the context of the relative low prevalence of the condition and the low mortality rates, such studies will require large numbers of patients and prolonged follow-up, suggesting that they are unlikely to materialise outside the context of publicly funded, multinational collaboration. Recently, Dybro et al[10] investigated the effects of metoprolol on LVOT obstruction, symptoms, and exercise capacity in oHCM in a double-blind, placebo-controlled randomised crossover study. Compared to placebo, metoprolol therapy reduced LVOT obstruction at rest and during exercise, provided symptom relief and improved

quality of life. However, maximal exercise capacity was unchanged, and the trial was not designed to look at survival benefit.

In agreement with cumulative evidence, the study by Javidgonbadi et al[6] suggests considerable sex-related differences in oHCM. It is evident that there is room for significant improvement in the management of females with oHCM. This must start with improved awareness and recognition of the condition in females to reduce time to diagnosis, followed by appropriate, evidence-based management (central illustration). Potential solutions include, addressing sex and gender specific challenges posed by social, cultural and economic aspects in the delivery of care to patients with HCM; broadening the diagnostic criteria, whereby an absolute maximal wall thickness of 13-14mm in a female may facilitate early disease surveillance and diagnosis; use of normalised wall thickness measurements in everyday clinical practice; developing sex-specific risk stratification models which go beyond the risk of SCD and address the broader HCM-related mortality and progression of heart failure; and promote appropriate genetic testing to facilitate early familial screening. Above all, similar to the study of Javidgonbadi et al,[6] females must be well represented in HCM studies which in tandem can facilitate a sex-specific evidence base and ensure that females benefit from the survival and quality of life improvements conferred by the refinement of HCM treatments.

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Central illustration: Female Sex and Persistent Inequalities in the Care of Patients with Hypertrophic Obstructive Cardiomyopathy: A Call to Action

Figure legend: BSA, body surface area; CMR, cardiac MRI; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LVMWT, left ventricular maximal wall thickness; RCTs, randomized control trials

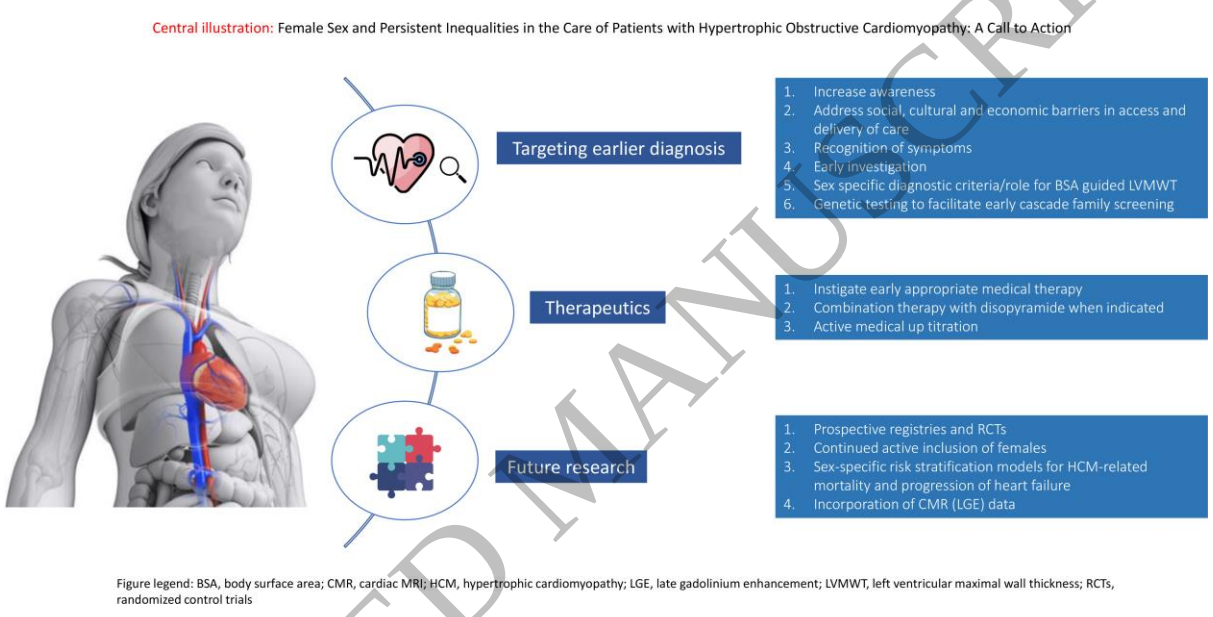

Figure 1
159x77 mm (.52 x DPI)