Sex differences in phenotypic expression and outcomes are well known in several cardiovascular conditions, including coronary artery disease, aortic stenosis, Takotsubo cardiomyopathy, and spontaneous coronary artery dissection, among others. These are attributable to genetic and hormonal differences, but also to variations in management and how men and women interact with the healthcare system. Recently, the issue of sex differences in the outcomes of hypertrophic cardiomyopathy (HCM) has gained the attention of several groups of investigators worldwide. In this issue of the *Journal of the American Heart Association* (*JAHA*), Rowin et al enrich this body of evidence with an important report from a well-established, large cohort of patients treated at an HCM center of excellence between 2001 and 2016. The investigators analyzed a data set of 2123 patients with HCM (38% women) and found that all-cause mortality was higher in women than men (9% versus 5%; *P* = 0.001) after a median follow-up of 3.9 years. However, there were no differences in HCM-related mortality and age-adjusted all-cause mortality between men and women, despite the fact that women were diagnosed and referred for subspecialty care later than men, more often had left ventricular outflow tract obstruction, had more severe symptoms at baseline, and more commonly developed advanced heart failure during follow-up.

### Overall Survival: Battle of the Sexes

As observed in the current cohort, where overall mortality was 6.4%, survival in HCM has improved in the current era. This likely relates to more accurate sudden cardiac death risk stratification and availability of advanced therapeutics, including septal reduction interventions and implantable defibrillators. However, despite these advances, not all patients with HCM experience excellent survival. Understanding which subsets of patients with HCM may benefit from alternative diagnostic, therapeutic, and/or monitoring approaches is critical. Rowin et al are to be commended for further investigating whether differences in survival and other clinical outcomes are present between women and men with HCM.

The findings of the current study are provocative and must be considered in the context of the study limitations and other recent HCM studies to fully appreciate their implications. As noted above, women in the study of Rowin et al were diagnosed and treated later than men and had worse clinical

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and echocardiographic profiles at baseline. This raises the question: why did the analysis fail to detect a difference in overall survival between men and women? The authors suggest that this may be caused by absence of sex-based biases in referral for advanced therapies (eg, surgical myectomy) in this cohort, coupled with data showing outcome equivalency after myectomy for women and men.8

The lack of a statistically significant difference in age-adjusted survival in the study by Rowin et al1 may reflect that there are no actual biological differences in mortality. However, it is important to consider what other studies conclude about survival in men versus women with HCM. In the Mayo Clinic study,2 female sex was associated with worse overall survival in univariate, multivariate, and propensity score–matched analyses. The multivariate hazard ratio of the association was 1.17 (95% CI, 1.07–1.25; P<0.001). More important, the result was not different when the analysis was further adjusted for the year of evaluation (effectively comparing men and women within their own treatment “eras”). Although the conclusions of the study of Rowin et al1 and our study from the Mayo Clinic HCM cohort seemingly differ, the study by Rowin et al1 has a smaller sample size (2123 versus 3673 patients), shorter follow-up (median, 3.9 versus 10.9 years), and lower event rate (0.01 versus 0.03 deaths/patient-year), likely reflecting a more modern era cohort. It is important to recognize, as the authors have, that this study is likely underpowered to detect a statistical difference in the event rates observed between women and men. Although the age-adjusted point estimate (hazard ratio, 1.32) is toward the direction associating female sex with worse survival, the large CI (0.92–1.91) is indicative of the significant uncertainty in the observed association. It is possible that with more person-years of follow-up and a larger number of events, these observed differences would reach statistical significance. Assuming \( \alpha=0.05 \), \( \beta=0.20 \), and women/men ratio 40:60, an ad hoc power calculation suggests that a total of \( \approx425 \) deaths would be required to detect a difference between the 2 groups with a relative hazard of 1.32 (as opposed to 135 deaths in the current analysis). Other confounders, such as differences in disease severity and comorbidities between the 2 populations, may explain the heterogeneous conclusions in the 2 studies.

In an earlier, 3-center study of 969 patients with HCM (n=393 women) reported in 2005, female sex was associated with progression to severe heart failure and death from heart failure or stroke, but not with overall mortality over an average follow-up of 6.2 years.4 In a later study of 621 HCM patients from China, enrolled between 1999 and 2001, female sex was independently associated with all-cause mortality, with a large magnitude of association (hazard ratio, 2.19; 95% CI, 1.21–3.95). Associations were also noted between female sex and excess risk for cardiovascular death and progressive heart failure.9 Most recently, in a large multicenter report of 4893 patients (36.1% women) of the European HCM Outcome Investigators’ collaboration between 1980 and 2013, 796 patients (16.3%) died after a median follow-up of 6.1 years.10 The investigators found excess mortality in women compared with men that persisted throughout the age spectrum in reference to expected mortality stratified by sex, country, and age. These last results have not yet been published in a peer-reviewed journal; therefore, they should be considered preliminary, pending a formal review process. However, in reviewing multiple sources, there continues to be a trend toward worse outcomes in female patients with HCM.

Other Important Findings

Rowin et al1 provide additional important insights about cause-specific mortality and other adverse cardiovascular events. The use of primary prevention implantable cardioverter-defibrillators was similar in men and women (25% and 24%, respectively) and was followed by similar rates of appropriate therapies for ventricular arrhythmias (\( \approx15\% \)). Although a detailed age group distribution of ventricular arrhythmia events is not provided, it is notable that age at first appropriate implantable cardioverter-defibrillator therapy was similar in women and men, despite women presenting with HCM at older ages. The incidence of the composite end point of appropriate implantable cardioverter-defibrillator therapies, resuscitated cardiac arrest, and sudden cardiac death was equally low in men and women (<1% per year).

In agreement with other reports,5,11 women in the study by Rowin et al1 experienced a higher burden of heart failure morbidity compared with men. Among women with obstructive HCM, 75% developed advanced heart failure symptoms as opposed to 56% of men (P<0.001), with rates of heart failure progression of 4.8%/year in women versus 3.4%/year in men. Among patients with nonobstructive HCM, women had twice as high rate of progression to advanced refractory heart failure symptoms compared with men (12% versus 6%; P=0.002).

One of the most noteworthy findings of the study by Rowin et al1 is a detailed analysis of the causes of death in the 70 women who died during follow-up (of 794 women included in the analysis). Only 1 in 5 deaths was considered attributable to HCM, predominantly caused by end-stage heart failure, whereas only 1 patient died of sudden cardiac death in the setting of left ventricular apical aneurysm, without an implantable cardioverter-defibrillator. Most deaths (n=57) were considered unrelated to HCM. There were no differences in men and women in regard to the relative incidence of HCM- and non–HCM-related deaths. However, the small number of events within the sex subgroups makes it difficult to draw firm conclusions.
Conclusions
Considering the current study in the context of the cumulative evidence from other larger studies, it is evident that differences in the course of disease exist between sexes. Sex should, therefore, be treated as a determining variable in all stages of the care of the patient with HCM, from disease awareness and diagnosis to risk assessment, follow-up, and management. Emphasis on sex-specific psychological and socioeconomic factors affecting the interface of patients with HCM with healthcare systems is likely to potentiate the survival and quality of life improvements conferred by the ongoing refinement of HCM therapeutics.

Disclosures
None.

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