

Sex, Survival, and Cardiomyopathy: Differences Between Men and Women With Hypertrophic Cardiomyopathy

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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 2016.¹ 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.

Sex Differences in HCM: What We Know

HCM has consistently shown a male predominance, with men comprising approximately 60% of most published HCM

cohorts,^{2–5} similar to the current study. Such male predominance is an unexpected observation, considering the autosomal dominant inheritance pattern of HCM, which should result in a balanced male/female ratio. This discrepancy may be partially explained by diagnostic bias and underrecognition of HCM in women. Accordingly, a key finding in the study by Rowin et al¹ is that women were older than men, on average by 6 years at the time of HCM diagnosis and at the time of referral for subspecialty evaluation. This is consistent with our experience in 3673 HCM patients (45% women) treated over a 37-year period and followed up for a median of 10.9 years. Women were, on average, 7 years older at the time of index evaluation.²

Women are also known to have a higher prevalence of the obstructive phenotype, worse diastolic function, and more severe heart failure symptoms at presentation.^{2,4} In the study by Rowin et al,¹ 73% of women had New York Heart Association class II to IV symptoms at presentation compared with 53% of men. Accordingly, women were significantly more likely to develop advanced drug-refractory heart failure (New York Heart Association class III/IV) compared with men at follow-up (53% versus 35%, respectively).

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^{6,7} 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 al¹ 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 al¹ 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 ≈ 425 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 ($\approx 15\%$). 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.

References

- Rowin EJ, Maron MS, Wells S, Patel PP, Koethe BC, Maron BJ. Impact of sex on clinical course and survival in the contemporary treatment era for hypertrophic cardiomyopathy. *J Am Heart Assoc*. 2019;8:e012041. DOI: 10.1161/JAHA.119.012041.
- Geske JB, Ong KC, Siontis KC, Hebl VB, Ackerman MJ, Hodge DO, Miller VM, Nishimura RA, Oh JK, Schaff HV, Gersh BJ, Ommen SR. Women with hypertrophic cardiomyopathy have worse survival. *Eur Heart J*. 2017;38:3434–3440.
- O'Mahony C, Jichi F, Ommen SR, Christiaans I, Arbustini E, Garcia-Pavia P, Cecchi F, Olivetto I, Kitaoka H, Gotsman I, Carr-White G, Mogensen J, Antoniadou L, Mohiddin SA, Maurer MS, Tang HC, Geske JB, Siontis KC, Mahmoud KD, Vermeer A, Wilde A, Favalli V, Guttman OP, Gallego-Delgado M, Dominguez F, Tanini I, Kubo T, Keren A, Bueser T, Waters S, Issa IF, Malcolmson J, Burns T, Sekhri N, Hoeger CW, Omar RZ, Elliott PM. International External Validation Study of the 2014 European Society of Cardiology Guidelines on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (EVIDENCE-HCM). *Circulation*. 2018;137:1015–1023.
- Olivetto I, Maron MS, Adabag AS, Casey SA, Vargiu D, Link MS, Udelson JE, Cecchi F, Maron BJ. Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;46:480–487.
- Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, Caleshu CA, Helms AS, Colan SD, Girolami F, Cecchi F, Seidman CE, Sajeev G, Signorovitch J, Green EM, Olivetto I. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the sarcomeric human cardiomyopathy registry (SHaRe). *Circulation*. 2018;138:1387–1398.
- Maron MS, Rowin EJ, Wessler BS, Mooney PJ, Fatima A, Patel P, Koethe BC, Romashko M, Link MS, Maron BJ. Enhanced American College of Cardiology/American Heart Association Strategy for prevention of sudden cardiac death in high-risk patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. 2019;4:644–657.
- O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2014;35:2010–2020.
- Meghji Z, Nguyen A, Fatima B, Geske JB, Nishimura RA, Ommen SR, Lahr BD, Dearani JA, Schaff HV. Survival differences in women and men after septal myectomy for obstructive hypertrophic cardiomyopathy. *JAMA Cardiol*. 2019;4:237–245.
- Wang Y, Wang J, Zou Y, Bao J, Sun K, Zhu L, Tian T, Shen H, Zhou X, Ahmad F, Hui R, Song L. Female sex is associated with worse prognosis in patients with hypertrophic cardiomyopathy in China. *PLoS ONE*. 2014;9:e102969.
- Lorenzini M. Excess mortality and sex differences in outcome in hypertrophic cardiomyopathy: a European multicentre study. DOTTORATO DI RICERCA in Scienze Cardio-Nefro-Toraciche. 2019. Alma Mater Studiorum – Università di Bologna. Available at: http://amsdottorato.unibo.it/8926/1/lorenzini_mssimiliano_tesi.pdf.
- Jang JH, Shin SH, Beak YS, Ko KY, Kwon SW, Park SD, Woo SI, Kim DH, Kwan J. Impact of gender on heart failure presentation in non-obstructive hypertrophic cardiomyopathy. *Heart Vessels*. 2019. DOI: 10.1007/s00380-019-01492-0.

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