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Response to letter regarding article "Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy: Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe)"

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The Sarcomeric Human Cardiomyopathy Registry (SHaRe) originates from international centers deeply invested in clinical investigation and state of the art management of hypertrophic cardiomyopathy (HCM). Unlike single center studies with relatively small patient cohorts and limited follow-up, the value of SHaRe lies in amassing the scale and diversity of patient experience needed to address fundamental questions regarding the natural history of this complex disease.

Our recent manuscript1 describes the lifetime burden of HCM from nearly 5,000 patients, spanning almost 25,000 patient-years. No other study has done this. We found that patients with early-onset HCM have more adverse outcomes in the ensuing decades than patients with late-onset HCM. All SHaRe sites have expert surgical programs that provide excellent myectomy outcomes. However, it is important to recognize that while myectomy provides highly effective symptomatic relief, it has never been proven to improve mortality, and as Dr. Maron and colleauges have reported,2 not all patients benefit. That the real burden of disease takes longer than previously appreciated to emerge – and emerges despite good treatment - is a novel finding from our study.

SHaRe provides an important step forward: a platform to address unresolved questions and unmet needs -- both of which remain substantial. Through multicenter collaboration, we

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demonstrated that genotype is informative of adverse natural history. Therefore, it is imperative to understand how sarcomere gene mutations cause profound abnormalities in myocardial energetics, contractile function, and cellular architecture. Additionally, the SHaRe study highlightes that some HCM, particularly non-familial HCM, carries a more favorable prognosis and may not require as aggressive management as sarcomeric HCM. Thus, it is crtitical to refine identification of clinically important and distinct subcohorts of HCM.

Finally, we are puzzled by the suggestion that our data might “adversely affect attitudes of clinicians”. We share Drs. Maron and Rowin’s optimism that HCM can be treated well with careful management. But equally so, we caution against underestimating the lifelong risks of HCM, particularly in younger patients. Over-emphasizing mid-term therapeutic successes will not prevent the emergence of chronic arrhythmias and heart failure. Indeed, progressive heart failure both in nonobstructive and obstructive HCM (despite myectomy) has been well-reported by Dr. Maron and colleagues, including subsets of patients (notably, younger patients with sarcomere mutations) experience greater morbidity and mortality despite their contemporary management.2–5 Moreover, only a minority of HCM patients benefit from the major advances in management championed by Dr. Maron and colleagues, specifically myectomy, life-saving implantable cardioverter defibrillator interventions, therapeutic hypothermia, or cardiac transplantation.2–5 The hard truth is that HCM, like other genetic cardiomyopathies, diminishes quality of life and survival. We can only substantively change natural history by understanding the fundamental mechanisms of disease and developing disease-modifying therapies. To mistake palliation for cure is inappropriate. Much remains to be learned and we hope that SHaRe continues to stimulate a call to action: To work collaboratively and tirelessly to target and correct the molecular abnormalities at the core of HCM, to improve the lives of our patients and families.

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Disclosures

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