

# The Evolving Story of Clinical Trials in Hypertrophic Cardiomyopathy

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*“Our greatest glory is not in never falling, but in rising every time we fall.”*

Attributed to Confucius

Thousands of papers on hypertrophic cardiomyopathy have been published since Donald Teare’s landmark description of the disease in 1958, but in spite of considerable advances in its management, clinicians still struggle with the treatment of symptoms in people afflicted by the condition. Patients with hypertrophic cardiomyopathy often complain of exertional chest pain, dyspnea and fatigue [1]. The underlying mechanisms are complex and vary between patients; in some, heart failure symptoms are caused by diastolic dysfunction with preserved ejection fraction and in others by systolic left ventricular dysfunction or left ventricular outflow tract obstruction (with or without mitral insufficiency). Atrial fibrillation is frequent in both scenarios and often exacerbates symptoms.

When caused by dynamic left ventricular outflow tract obstruction, exertional symptoms can be managed effectively with drugs or interventions such as surgical septal myectomy and alcohol septal ablation. However, treatment options in non-obstructive patients are usually much less successful and are often associated with side-effects. In this edition of the journal, Olivotto and colleagues report a multicenter, double-blind, phase 2 study of ranolazine—an inhibitor of the cardiac late sodium current ( $I_{\text{NaL}}$ )—in 80 adult patients with non-obstructive hypertrophic cardiomyopathy who were randomly assigned to placebo or ranolazine 1000 mg bid for 5 months [2].  $I_{\text{NaL}}$  is an inward membrane ion current that occurs predominantly during phase 2 and early phase 3 of repolarization. In normal cardiomyocytes, its contribution to the duration of the action potential is minimal, but in disease states  $I_{\text{NaL}}$  is increased causing intracellular  $\text{Na}^+$  overload and a decrease of the transmembrane electrical gradient that favors reversal of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger and cytosolic  $\text{Ca}^{2+}$  overload [3]. In a recent study of myocardial tissue removed at the time of septal myectomy,  $I_{\text{NaL}}$  was found to be  $\approx 2$ -fold greater in cardiomyocytes from patients with hypertrophic cardiomyopathy compared to those taken from control tissue [3]. This difference was associated with increased diastolic  $\text{Na}_i^+$  and  $\text{Ca}_i^{2+}$  concentrations, enhanced

susceptibility to triggered arrhythmias, hypercontractility, and increased diastolic tension, all of which were significantly reduced or abolished by ranolazine.

Based on these preclinical findings, ranolazine might be expected to improve diastolic dysfunction and microvascular perfusion and to reduce ventricular arrhythmias in hypertrophic cardiomyopathy. Sadly, in this well conducted randomized trial, ranolazine showed no effect on exercise performance, plasma pro-brain natriuretic peptide levels, diastolic left ventricular function or quality of life. This finding adds to a rather depressing lack of efficacy in other studies [4] and the premature termination of trials examining a novel late sodium current inhibitor, eleclazine [5], and the drug perhexiline [6].

Nevertheless, Olivetto and colleagues are to be congratulated on overcoming the considerable challenges involved in conducting a randomized trial in hypertrophic cardiomyopathy in the first place. Although not a rare disease by most current definitions, hypertrophic cardiomyopathy shares with them a number of features that present obstacles to the conduct of randomized trials including a heterogeneous clinical phenotype and small patient populations clustered in a few tertiary care centers. The randomized controlled trial is the reference standard for establishing clinical efficacy of investigational products as it minimizes selection bias, distributes confounders between study groups and limits investigator and participant bias in the assessment of outcomes. However, this classical approach to clinical trial design is costly, time-consuming, and often requires large sample sizes to uncover small therapeutic effects— all of which are problematic in uncommon diseases such as hypertrophic cardiomyopathy.

A second fundamental issue is the selection of end-points. Like many rare disorders, hypertrophic cardiomyopathy is a chronic disorder that evolves slowly over decades and while it is associated with death from ventricular arrhythmia and heart failure, the annual event rates even in tertiary center populations are low. This means that conventional hard end-point trials are difficult to design, a fact recognized by licensing authorities who increasingly seek validated measures of disease activity or disease progression as surrogate markers of efficacy in rare diseases.

In this study, the primary end-point was a change in peak oxygen consumption. When performed by experienced personnel, cardiopulmonary exercise testing with

simultaneous measurement of respiratory gases is an objective measure of functional limitation [7]. Studies in patients with hypertrophic cardiomyopathy have shown that cardiopulmonary exercise testing can aid differential diagnosis and predict clinical outcomes, in particular heart failure [8]. However, its value as a surrogate end-point for response to an intervention requires further study as the complex mechanism of exercise limitation in hypertrophic cardiomyopathy is such that it might be possible to reduce symptoms—for example by alleviating exercise induced myocardial ischemia or reducing elevated filling pressures—without changing left ventricular stroke volume or cardiac output, necessary prerequisites for an improvement in peak oxygen consumption. One alternative might be to use patient reported symptoms instead but these are often dismissed as too subjective for the purposes of trials. However, this seems somewhat paradoxical given that they are regarded as sufficiently robust in real world clinical practice to select patients for sometimes risky interventions.

In spite of the many challenges of performing trials in hypertrophic cardiomyopathy, there are grounds for optimism about the future. The problem of cohort size is being solved by the development of international collaborations that provide the basis for larger trials powered to detect reductions in hard end-points [9]. There is also growing appreciation of the limitations of treating all patients as if they have the same disease. Hypertrophic cardiomyopathy is an umbrella term that encompasses a wide range of genetic and non-genetic diseases and as patient cohorts increase in size and genotyping becomes mainstream, there is an increasing focus on specific therapeutic targets that might form the basis of a more bespoke approach to therapy. The critical message from this paper is that we owe it to patients to continue the effort to discover new approaches to symptom management and ultimately the prevention of disease progression.

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