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## Review

# Hypertrophic cardiomyopathy: The need for randomized trials

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**ABSTRACT**

Hypertrophic cardiomyopathy (HCM) is a complex cardiac condition characterized by variable degrees of asymmetric left ventricular (LV) hypertrophy, generally associated with mutations in sarcomere protein genes. While generally perceived as rare, HCM is the most common genetic heart disease with over one million affected individuals in Europe alone and represents a prevalent cause of sudden cardiac death in the young. To date, HCM remains an orphan disease, as recommended treatment strategies are based on the empirical use of old drugs with little evidence supporting their clinical benefit in this context. In the six decades since the original description of the disease, less than fifty pharmacological studies have been performed in HCM patients, enrolling little over 2,000 HCM patients, mostly comprising small non-randomized cohorts. No specific agent has been convincingly shown to affect outcome, and critical issues such as prevention of myocardial energy depletion, microvascular ischemia, progressive myocardial fibrosis and the peculiar mechanisms of arrhythmogenesis in HCM still need to be addressed in a systematic fashion. However, there is increasing evidence that a variety of drugs may counter the effects of sarcomere protein mutations and the resulting pathophysiological abnormalities at the molecular, cellular and organ level. Following major advances in our understanding of HCM and increasing opportunities for networking among large international referral centres, the opportunity now exists to identify potentially effective treatments and implement adequately designed pharmacological trials, with the ultimate aim to impact the natural course of the disease, alleviate symptoms and improve quality of life in our patients.

**Keywords:** hypertrophic cardiomyopathy, translational research, pharmacological therapy, clinical trials, outcome

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**Figure 1. Levels of therapeutic intervention: towards the core.**

Imagining a disease as a fruit or a planet, there are several levels at which one can intervene with any therapeutic approach (Figure 1). The first and most obvious is to simply scratch the surface and control symptoms. This objective can be achieved in most cardiac patients: however, it is the very least that we can do. The second step is to interfere and possibly halt disease progression, thus preventing its consequences on outcome: this can be done in several cardiac conditions, but is definitely harder to achieve.<sup>1,2</sup> Third, we can try to prevent the development of full-blown disease in patients who are predisposed due to acquired risk factors and/or genetic substrate.<sup>3</sup> And fourth, we can address the core of the problem by acting directly on the etiology, removing the actual cause and ultimately cure the patient.<sup>1,4</sup> Despite extraordinary progress over the last decades, these last two steps have hardly if ever been achieved in cardiovascular medicine.

As a consequence, it is important to realize that our practice is based on highly sophisticated palliation. What this approach usually does is change a disease into a milder one. For example, septal myectomy turns obstructive into non-obstructive hypertrophic cardiomyopathy (HCM), a highly significant change for the patient.<sup>5,6</sup> Therefore, this kind of very effective palliation is something we should definitely keep on doing and improving until a cure becomes available.<sup>2</sup> However, all efforts should be directed at improving the state of things by accumulating new evidence and knowledge.<sup>4,7</sup>

### **HYPERTROPHIC CARDIOMYOPATHY AS AN ORPHAN DISEASE**

HCM is a complex cardiac condition characterized by variable degrees of left ventricular (LV) hypertrophy occurring in the absence of secondary triggers, generally associated with mutations in sarcomeric protein genes.<sup>2,5</sup> Although perceived as rare, HCM is the most common genetic heart disease, as well as a prevalent cause of sudden cardiac death in the young. Based on the reported prevalence of 1:500 in the general population, a total estimate exceeding one million individuals with HCM are expected in Europe alone. HCM is characterized by a very complex pathophysiological background that accounts for the heterogeneity of its clinical manifestations and natural history.<sup>5</sup> Established features of the disease, besides left ventricular (LV) hypertrophy, include a constellation of deranged cardiomyocyte energetics, diastolic dysfunction, microvascular ischemia, enhanced myocardial fibrosis, autonomic dysfunction and enhanced arrhythmogenesis.<sup>8,9</sup> In addition, most patients exhibit dynamic LV outflow tract obstruction either at rest or with physiological provocation.<sup>10</sup> Outflow obstruction is a major determinant of symptoms, such as dyspnea, chest pain or presyncope and, together with sudden death prevention, has represented the most visible and consistent target of therapeutic efforts in HCM.<sup>2,5-7</sup>

Despite decades of increasing attention and research efforts by the scientific community, treatment strategies for HCM remain largely based on a small number of clinical studies, or empirically based on personal experience or extrapolation from other cardiac conditions. As stated in the recent Report of the Working Group of the National Heart, Lung, and Blood Institute on Research Priorities in Hypertrophic Cardiomyopathy,<sup>7</sup> “nearly 50 years after the identification of HCM as an autosomal dominant disease, and 20 years after its linkage to sarcomeric protein mutations, we still do not understand the most proximal mechanism(s) that initiates the disorder”; and “treatment recommendations in HCM are based on observational series without prospective randomized controls. While clinical usage provides support that various pharmacologic agents reduce HCM symptoms, no evidence has demonstrated that they alter disease progression or outcomes.”

In a recent review of original articles, reviews and editorials addressing any pharmacological agent ever used in HCM cohorts, only forty-five studies were identified over the last sixty years (i.e. less than 1 per year), enrolling a total of 2,121 HCM patients.<sup>4</sup> Of these, only 5 were randomized double blind

placebo-controlled trials. Remarkably, a comparison of the period 1991–2011 vs. 1971–1990 demonstrated no increase in the number of studies, and only a modest increase in the number of patients enrolled (627 vs. 1,473, patients respectively). With regard to sample size, only 7 studies (15%) enrolled more than 50 patients, whereas 22 (49%) had less than 20 patients.<sup>4</sup> The maximum number of patients in a single prospective study was 118, in a multicenter registry evaluating the efficacy and safety of disopyramide.<sup>11</sup> Overall, these data eloquently demonstrate how poorly pharmacological research in HCM compares with that performed in other, more prevalent conditions such as coronary artery disease and heart failure.<sup>1</sup>

Notably, when randomized trials have been performed in HCM, results have been far less intuitive than expected. The story of dual-chamber pacing for control of LV outflow obstruction is certainly the best case in point. Based on anecdotal observations showing an effect of LV pacing on obstruction, several and often intriguing pathophysiological explanations were provided, leading to three randomized trials. All three showed that pacing had in fact little if any effect on the gradient or exercise capacity in most patients, and that any improvement in symptoms was largely related to a placebo effect of the device.<sup>5,12</sup> Thus, we should be aware that several widely accepted recommendations for management of HCM based on expert opinion or case series still need to stand the test of properly designed trials.

### INHERENT CHALLENGES OF CLINICAL TRIALS IN HCM

Several reasons – some obvious, other less so – stand behind this state of things. The first lies with the practical challenges inherent in designing trials with HCM patients (Table 1). The epidemiology of HCM is complex and as yet only partially resolved, due to issues such as incomplete penetrance and prevalence of subclinical disease.<sup>3,13</sup> Despite not being rare, HCM is uncommonly encountered and possibly neglected at many community-based cardiac centers and outpatient clinics. Furthermore, even when overt and correctly diagnosed, its clinical spectrum is highly heterogeneous, encompassing different stages that may not be directly comparable.<sup>9</sup> A preventive trial in genotype-positive/phenotype-negative individuals will necessarily enroll subsets that are different from HCM patients with classic phenotype and dynamic outflow obstruction, or in the end-stage phase. Each research question should be addressed by targeting the appropriate patient subgroups, with imaginable problems in achieving the desired yield in any given cohort.<sup>7,9</sup>

Another very complex issue concerns the assessment of outcome in HCM, and the effects of treatment on survival. Even at tertiary referral centers, cardiovascular mortality rates in contemporary HCM cohorts are very low, i.e. 1–2%/year, although the selected subset with systolic dysfunction and end-stage progression may exceed 10%/year.<sup>2,5,9,14</sup> Rates of sudden cardiac death, formerly believed to be very common among HCM patients, are even lower, i.e. <1% in most cohorts and only 3%/year even in patients carrying implantable defibrillators because judged to have a “high-risk” status.<sup>15</sup> Based on these estimates, large patient cohorts and extended follow-up duration are required to detect differences in survival, even when a highly effective drug or procedure is tested. Thus, the relatively favorable long-term prognosis of most HCM patients may represent a formidable obstacle to clinical trials targeting outcome, including a hypothetical study comparing surgical myectomy and percutaneous alcohol septal ablation.<sup>16</sup>

In order to overcome the limitations associated with the low hard event rates, surrogate end-points have often been employed in HCM trials, including indexes of LV performance, functional capacity and oxygen consumption, progression of symptoms, prevalence of arrhythmias and appropriate

**Table 1. Challenges for clinical trials in HCM.**

Relatively low prevalence (1:500)	Need for adequate networking, hard to perform single-center trials
Heterogeneous disease spectrum	Need to tailor trials to specific subsets, hard to include all patients in a single study
Low event rates	Difficult to power studies to assess differences in survival/hard outcome end-points
Surrogate end-points	End-points such as oxygen consumption, variation in symptoms, regression of LV hypertrophy or arrhythmias may be difficult to define and/or have an uncertain relation to outcome
Complex, unresolved pathophysiology	Need to identify appropriate targets for treatment
Perceived as economically irrelevant to the pharmaceutical industry	However, this is a wrong perception based on absolute number of patients and need for very extended treatment

defibrillator shocks, circulating markers of collagen synthesis and natriuretic peptides.<sup>4,13,17–19</sup> Advanced imaging techniques such as positron emission tomography (PET) and cardiac magnetic resonance (CMR) can be exploited today to quantify the effect of novel treatments on relevant features including coronary microvascular dysfunction and tissue fibrosis, respectively.<sup>13,20–23</sup> Each of these may represent reasonable end-points in certain contexts, particularly in proof-of-concept and pilot studies. Furthermore, pilot studies based on these surrogate end-points might provide the rationale and justify the effort of large, multicenter, prospective studies enrolling the number of patients necessary to determine the benefit of novel treatments on more robust measures of outcome.<sup>4,7</sup> At the same time, the favourable long-term prognosis associated with HCM identifies control of symptoms and improvement in quality of life as major objectives for pharmacological treatment, to be pursued and investigated independent of outcome.<sup>4</sup>

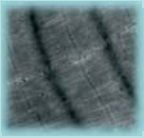
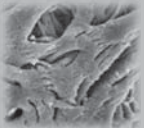
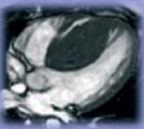
Last but not least, HCM has never been the focus of strong economic interest by pharmaceutical companies, because of the perceived rarity of the disease as well as the lack of novel and expensive therapeutic agents such as have been approved, for example, in rare conditions such as Fabry disease or pulmonary arterial hypertension.<sup>24</sup> This aspect, however, may be expected to change soon. In recent years, the widespread use of imaging and genetic testing for familial screening, as well as an increasing awareness in the medical community, have led to the identification of large HCM populations, regularly followed at international referral centers.<sup>24</sup> For the first time in the history of this disease, it has become feasible to address HCM management issues in an evidence-based fashion, by means of adequately designed clinical trials. The full exploitation of this potential may lead to a paradigm shift in research methodology involving the whole field of genetic heart diseases. Such favorable conjunction is beginning to attract the interest of private companies, promoting investments that are likely to reach a critical mass for effective clinical research in a very near future.<sup>4,25</sup> When this time comes, the powerful combination of basic science, clinical knowledge and adequate trial methodology may finally come to fruition.

## POTENTIAL TARGETS OF PHARMACOLOGIC TREATMENT

Progress in HCM treatment is hindered by the incomplete knowledge of its pathophysiologic mechanisms and lack of specific agents capable of interfering with disease-causing pathways.<sup>7–9</sup> However, several targets for treatment have been identified (Figure 2), some of which overlap with other cardiac diseases and with heart failure at large.<sup>8,26</sup> For example, interventions aimed at normalizing energy homeostasis represent a viable approach, as shown by a recent study on perhexiline, a metabolic modulator which inhibits the metabolism of free fatty acids and enhances carbohydrate utilization by the cardiomyocyte. In a recent randomized double-blind placebo-controlled trial, perhexiline has shown the capacity to improve the energetic profile of the LV, resulting in improved diastolic function and exercise capacity in HCM patients.<sup>18</sup>

Furthermore, HCM cardiomyocytes exhibit well-established abnormalities in intracellular calcium handling, contributing to excessive energy expenditure and enhanced arrhythmogenesis that are largely due to enhanced membrane late sodium current.<sup>26</sup> Such defect may be selectively and dramatically reversed *in vitro* by ranolazine.<sup>26</sup> Following the demonstration of its beneficial effects on HCM cardiomyocytes, a multi-center, double blind, placebo-controlled pilot study is currently underway in Europe to test the efficacy of ranolazine on exercise tolerance and diastolic function in symptomatic HCM patients (RESTYLE-HCM; EUDRA-CT 2011-004507-20). Besides the specific merits of ranolazine, similar examples of translational approach to HCM identifies a fundamental pre-requisite for the identification of novel, potentially effective agents, based on thorough investigation of the molecular basis of the disease.<sup>1</sup> In the future, a more specific approach may be tailored to specific mutations or groups of mutations, by screening large panels of candidate molecules in assays based on induced pluripotent stem cells isolated from human fibroblasts.<sup>27</sup> As shown recently, the possibility of modulating the activity of sarcomere contractile proteins, such as beta-myosin, is beginning to surface, with huge potential implications for HCM treatment.<sup>28</sup>

Finally, an option that is less seductive but should not be underestimated, is to investigate potential role in HCM patients of drugs that represent the standard of care for other cardiac patients. Agents such as modulators of the renin-angiotensin system, statins and calcium antagonists have all shown promise in preventing development of LV hypertrophy in genotype positive individuals,<sup>3</sup> and may potentially normalize cellular homeostasis, prevent microvascular remodeling and ischemia, reduce fibrosis and prevent end-stage progression.<sup>4,8,9,17,21,22</sup> However, the indications, timing and doses of

LEVEL OF INTERVENTION	TARGET	GOAL
<b>MOLECULAR</b> 	Abnormal Sarcomere Function Enhanced Ca <sup>++</sup> Sensitivity Unfavourable EP Remodeling	Improve Contractile Efficiency Inhibit Triggers for LVH Reduce Arrhythmogenesis
<b>CELLULAR</b> 	Deranged Energy Homeostasis Disturbed Biomechanical Stress Sensing Abnormal Ca <sup>++</sup> Handling	Prevent Energy Depletion Prevent Hypertrophy/Apoptosis Control Collagen Synthesis
<b>ORGAN</b> 	Microvascular remodelling Myocardial Fibrosis Diastolic Dysfunction Reentry Arrhythmias	Reduce Myocardial Ischemia Preserve Systolic Function Improve Diastole Prevent Arrhythmias

**Figure 2. Therapeutic targets and goals in HCM.**

these treatments remain unresolved in HCM, and their efficacy in impacting its natural history remains untested. Likewise, the effects of betablockers and antiarrhythmics, such as amiodarone, in preventing appropriate defibrillator shocks and sudden cardiac death has only been addressed retrospectively and inconclusively.<sup>29</sup> As noted above, many recommendations present in current HCM guidelines still require adequate evidence to their support, including several that few would dare question. And while it is unrealistic to expect that each of these indications will become evidence-based in the near future, it is the change of attitude that really matters, from passive acceptance of the empirical to uncompromising quest for the methodologically appropriate and convincing.<sup>2,4,7</sup>

## CONCLUSIONS

HCM is not uncommon, but remains an orphan disease with regard to pharmacological treatment. In the era of translational research, physicians and researchers have been very good at asking the right questions, but need to direct more effort into finding the best clinical answers for HCM patients. In a broader perspective, cardiomyopathies should be seen as paradigms providing invaluable insights on disease mechanisms that may be of general relevance to patients with more prevalent cardiac conditions. What has long been considered impossible to achieve is now closer at hand: the time is now ripe to promote robust clinical research in this complex condition in order to advance and standardize management of HCM patients.

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