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Lessons from the trials

INHERIT (INHibition of the renin angiotensin system in hypertrophic cardiomyopathy and the Effect on hypertrophy—a Randomised Intervention Trial with losartan)

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ABSTRACT

Early pharmacological interventions on transgenic models of hypertrophic cardiomyopathy (HCM) using angiotensin receptor blockers (ARBs) may be effective in preventing development of clinical phenotype or causing phenotype regression in early stages of disease. In the clinical setting, however, the effects of ARBs on HCM phenotype have been less consistent. INHERIT (INHibition of the renin angiotensin system in hypertrophic cardiomyopathy and the Effect on hypertrophy—a Randomised Intervention Trial with losartan) was designed to assess the effect of 100 mg of losartan in promoting the regression of LV hypertrophy in HCM. The primary end-point of the study was the reduction in LV mass assessed by MRI or computed tomography. After 12 months, no reduction in LV mass was observed in the losartan arm, and there was no difference in LV mass change with the placebo arm. The same was true for all secondary endpoints. The implications of these findings are discussed in the light of further, ongoing study targeting the HCM phenotype.

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BACKGROUND

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, with prevalence in the general population of 1:500, and represents an important cause of cardiovascular morbidity and sudden cardiac death in young individuals.^{1–2} HCM is caused by mutations in genes coding cardiac sarcomere proteins such as myosin binding protein C and beta-myosin heavy chain, generating complex pathophysiological manifestations, which ultimately translate into a heterogeneous spectrum of morphological and clinical phenotypes.³ While the disease is defined by the presence of asymmetric left ventricular (LV) hypertrophy, features such as impaired cardiomyocyte energetics, increased calcium sensitivity, microvascular ischemia, myocardial fibrosis, diastolic dysfunction, dynamic LV outflow obstruction, atrial fibrillation and ventricular arrhythmias are all part of the disease spectrum, representing established or potential targets for treatment.^{2,4}

Pharmacological interventions in patients with HCM are often necessary for control of symptoms, arrhythmias and obstruction. However, currently available strategies are based on time-honoured experience or extrapolation from other cardiac conditions, rather than robust and disease-specific evidence. Thus, HCM largely remains an orphan disease.^{3,4}

Increasing awareness in the cardiology community and widespread use of imaging and next generation sequencing approaches to genetic testing have allowed the identification of large populations of individuals with HCM, and the multiplication of centers of excellence worldwide.¹ At the same time, animal studies on transgenic models of HCM have led to the validation of novel, promising treatment strategies.³ As a result, the opportunity now exists to implement adequately designed pharmacological trials in HCM, using established as well as novel drug therapies, to potentially intervene on the complex pathophysiology of the disease and alter its natural course. There are, however, important challenges associated with the design and implementation of clinical trials in HCM. These include the relative rarity of the disease, its heterogeneous presentation and course (with radically different clinical profiles and treatment priorities in the different stages), low rates of cardiovascular events, the uncertain value of surrogate end-points and limited economic interest from the pharmaceutical industry.⁴ Despite these obstacles, well-conducted studies on HCM are proliferating, suggesting that the world of genetic cardiomyopathies is about to become evidence-based.^{4–6} The recently published INHERIT (INHibition of the renin angiotensin system in hypertrophic cardiomyopathy and the Effect on hypertrophy—a Randomised Intervention Trial with losartan), represents an important step in the right direction, despite its negative findings.⁷

RATIONALE: ROLE OF ARBS IN THE PREVENTION OF HCM

In recent years, evidence has accumulated that early pharmacological interventions on transgenic HCM models may be effective in preventing development of a clinical phenotype or causing phenotype regression in early stages of disease, as well as preventing fibrosis. Several agents have been effective in this regard and include angiotensin receptor blockers (ARBs), statins, spironolactone, calcineurin inhibitors, N-acetylcysteine and diltiazem.^{4,8} The activation of transforming growth factor-beta 1 seems to represent a critical step in the generation of myocardial fibrosis in animal models of HCM. Its inhibition by angiotensin receptor blockers (ARBs) in transgenic mice with sarcomere mutations translated into a measurable benefit in terms of phenotypic evolution and development of disease, although overt disease could not be regressed.⁹

In the clinical setting, however, the effects of ARBs on HCM phenotype have been less consistent. Small pilot studies enrolling 20 to 30 patients each have shown a decrease in left ventricular mass following treatment with candesartan and losartan,^{10,11} although other, comparable studies showed little or no effect of treatment on LV hypertrophy.^{12,13} In the study by Shimada et al, a small reduction in fibrosis was observed, i.e. a 0.7 mL decrease in the losartan group versus a 0.5 mL increase in the placebo group.¹³ These observations represented a strong rationale for a larger study assessing the effects of ARBs on LV mass and myocardial fibrosis in a randomized HCM population. Indeed, cardiac magnetic resonance imaging (MRI) studies have demonstrated that the degree of LVH can be reduced by septal reduction interventions such as surgical myectomy or percutaneous alcohol septal ablation, reflecting a remodeling process affecting LV regions remote from the septum and suggesting a reversible quota of LV hypertrophy in adult patients.^{14,15}

Furthermore, a study by Todiere et al has recently shown that HCM is a dynamic disease, in which myocardial fibrosis may progress rapidly, to an extent that variations are measurable within time intervals that are reasonable for a clinical trial.¹⁶ Based on these promising pieces of evidence, INHERIT

was designed to assess a potential effect of losartan in promoting regression of LV hypertrophy and fibrosis in HCM.⁷

DESCRIPTION OF TRIAL

INHERIT is a single-centre, randomised, double-blind, placebo-controlled study performed at the Unit for Inherited Cardiac Diseases of the University of Copenhagen, Denmark, aiming to assess the effects of 100 mg of losartan, administered for 12 months in adult HCM patients.⁷ The primary end-point of the study was the reduction in LV mass indexed to body surface area, as assessed by MRI or, in patients with implantable defibrillators or pacemakers, computed tomography (CT). Secondary endpoints included changes in burden of LV fibrosis as assessed by late gadolinium enhancement (LGE) on MRI, maximum LV wall thickness, left atrial volume and plasma levels of NT-pro-BNP. The authors initially calculated a sample size of 320 patients, in order to include 40 patients in each of eight pre-specified subgroups (patients with resting LV outflow tract obstruction, with known mutations in genes coding for sarcomere proteins; with an ICD; with prior alcohol septal ablation or septal myectomy; with borderline HCM; with extreme hypertrophy; younger than 40 years and with a history of hypertension). However, initial recruitment for the study was slow, and a large number of screening failures was reported, mostly due to pre-existing treatment with ARBs or ACE-inhibitors. Thus, the statistical plan was revised and a sample size of 132 patients was recalculated as sufficient to detect a change in LV mass of 12 g/m² with a power of 90%, a two-sided α of 5%, and allowing for 10% withdrawals. Analysis of pre-specified groups was still performed, but considered to be hypothesis-generating only. Importantly, this was an independent study supported by the Capital Region of Denmark, the Rigshospitalet Research Fund and other no-profit associations.

INHERIT ultimately enrolled 133 HCM patients, 69 in the placebo and 64 in the losartan arm; mean age was 52 years, and there was a 75% male predominance. Of these, 124 (93%) completed the study and were included in the intention-to-treat analysis. Patient compliance was good, as documented by the fall in arterial blood pressure in the treatment arm; expectedly, patients on active treatment were more likely to complain of side-effects and withdraw from the study. Overall, however, treatment with losartan at the target dose of 100 mg was generally well tolerated: among patients with resting LV outflow obstruction, who were observed in hospital for 6-hours after the initial dose due to concerns with hemodynamic instability, no adverse events were reported, and only one obstructive patient on active treatment showed worsening of symptoms during follow-up.

Specifically, among the 72 patients in whom LGE was quantitatively assessed, 60 showed evidence of myocardial fibrosis at baseline and 5 developed LGE during follow-up. Neither the change in extent nor *de novo* occurrence of LGE differed between the two treatment arms. Of note, both groups showed significant increase in total LGE, expressed as percentage of total LV mass (from 3% to 7% in the placebo group, and from 2% to 6% in the losartan arm, between group difference $p = 0.62$), confirming the dynamic nature of HCM pathophysiology. Changes in left atrial dimension, maximum LV wall thickness and NT-ProBNP levels were also similar in the two groups ($p = 0.26$, 0.69 and 0.67 , respectively).

With regard to the methodology used for LV mass evaluation, 61% of the study patients were assessed by MRI and 39% by CT at baseline; at 12 months, 3 patients crossed over to CT because of ICD implantation during the study period. In order to assess intermodality agreement, 20 patients underwent both CMR and CT at 12-month follow-up. Mean left ventricular mass was slightly but significantly underestimated by CT, compared to CMR, by an average of 13 grams ($p = 0.02$) - a difference roughly equivalent to the primary end-point used in power calculations. However, 98% of 124 patients were assessed with the same technique at baseline and follow-up.

CRITIQUE & DISCUSSION

Several conclusions may be drawn from the INHERIT. The first is that adequately designed randomized trials are feasible in genetic cardiomyopathies.⁴⁻¹⁷ Despite difficulties with enrollment, the authors were able to enroll their large sample in a single center over reasonable time, and patient compliance during follow-up period was very good. This success strongly suggests that a multicenter design might allow adequate evaluation of other, even more ambitious end-points in HCM populations, including exercise capacity, surrogate markers of heart failure or sudden death and, hopefully, outcome.⁴ The second is that ARB therapy is very safe in HCM patients, even in the presence or dynamic outflow obstruction, and may be employed for treatment of concomitant hypertension or coronary disease.¹⁸

On the negative side, the neutral effects of losartan with regard to all the end-points argues against the use of ARBs as a long-term therapy capable of altering the HCM phenotype and natural history, at least in patients with fully developed disease. After all, animal models of HCM may not faithfully recapitulate the response to therapy observed in humans, and the role of transforming growth factor-beta 1 may be less relevant in the latter.⁹ These conclusions hold, of course, if the power calculation of INHERIT is deemed appropriate to definitely settle the issue.

One might argue, however, that the study design was overambitious when compared with regression of hypertrophy observed, for example, in patients with severe hypertension;¹⁹ although the required sample size may never be achievable in HCM studies.²⁰ Likewise, duration of follow-up may have been one of INHERIT's Achilles' heels: in order to observe a measurable reduction in genetically-driven LVH developing over decades, a 12-month treatment course may have been simply too short. Indeed, while the aforementioned MRI studies following invasive septal reduction therapies have shown significant reduction of hypertrophy in similar time frames, they have likely benefitted from the acute effect exerted by the relief of obstruction in rapidly reversing a quota of "secondary" LVH.^{14,15} Such advantage could not be exploited in the INHERIT, and it is possible that longer observation times may be required to observe a comparable effect by pharmacological interventions in HCM hearts. The data on myocardial fibrosis, however, suggests that larger and longer studies are unlikely to show different results in this disease. As noted, there was measurable increase in LGE over the study period in both arms of INHERIT. Thus, treatment with losartan at full therapeutic doses failed not only to revert, but even to block progression of disease over the 12 months.

WHAT HAVE WE LEARNED?

The results of INHERIT argue against the capability of ARBs to interfere with the complex pathophysiology of HCM once the disease is fully developed, suggesting that earlier stages of disease should be targeted in hopes of reproducing the promising pre-clinical data.⁹ Residual hope for an ABR-based strategy now lies with the ongoing VANISH trial, targeting individuals with HCM-causing mutations but no or only initial phenotypes, in hopes of preventing disease development, rather than regression as in INHERIT. Notably, a recently published trial double-blind pilot trial in sarcomere mutation carriers without LV hypertrophy showed that diltiazem – another agent associated with prevention of disease in transgenic HCM models,⁸ promoted favourable LV remodeling by attenuating longitudinal decrease in LV cavity size and preserving LV thickness-to-dimension ratio.⁶ The authors postulate that such geometric changes may have a greater functional impact than reflected by simple linear measurements, and improve LV compliance.⁶ Future perspectives include the possibility of preventing the disease by allele-specific silencing or exon skipping techniques.^{21,22}

In adult patients with full-fledged HCM, however, the quest for agents capable of reversing the disease process remains arduous, and it appears more remunerative to search for agents capable of mitigating the metabolic, energetic and functional consequences of sarcomere mutations. Approaches under investigation include metabolic modulators such as perhexiline and late sodium current inhibitors.^{4,5} The RESTYLE-HCM study, testing the effects of ranolazine on exercise capacity in symptomatic HCM patients, has just been completed, and the LIBERTY-HCM trial, employing a novel and more potent late sodium current inhibitor specifically developed for patients with HCM and long QT syndrome, is ongoing.⁴ Whatever the outcome of these studies, a new era has irreversibly begun. Time is ripe for adequately designed and powered investigations towards an evidence-based, disease specific treatment of HCM.²³

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