Controversies in cardiovascular medicine

Pharmacological treatment options for hypertrophic cardiomyopathy: high time for evidence

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Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, affecting over one million individuals in Europe. Hypertrophic cardiomyopathy patients often require pharmacological intervention for control of symptoms, dynamic left ventricular outflow obstruction, supraventricular and ventricular arrhythmias, and microvascular ischaemia. Current treatment strategies in HCM are predicated on the empirical use of long-standing drugs, such as beta-adrenergic and calcium blockers, although with little evidence supporting their clinical benefit in this disease. In the six decades since the original description of the disease, <50 pharmacological studies enrolling little over 2000 HCM patients have been performed, the majority of which were small, non-randomized cohorts. As our understanding of the genetic basis and pathophysiology of HCM improves, the availability of transgenic and preclinical models uncovers clues to novel and promising treatment modalities. Furthermore, the number of patients identified and followed at international referral centres has grown steadily over the decades. 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. Therefore, it is timely to review the available evidence for pharmacological therapy of HCM patients, highlight the most relevant gaps in knowledge, and address some of the most promising areas for future pharmacological research, in an effort to move HCM into the era of evidence-based management.

Keywords
Hypertrophic cardiomyopathy • Pharmacological treatment • Outcome • Randomized trials

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease,1–7 with a prevalence in the general population of 1:500, i.e. an estimate of > 1 000 000 affected individuals in Europe, representing a leading cause of sudden cardiac death in the young3 and a prevalent cause of heart failure and stroke.1 Hypertrophic cardiomyopathy is characterized by a very complex pathophysiological background, reflecting into heterogeneous clinical manifestations and natural history. Established features of the disease include a constellation of asymmetric left ventricular (LV) hypertrophy, deranged cardiomyocyte energetics, diastolic dysfunction, microvascular ischaemia, enhanced myocardial fibrosis, abnormal sympathetic innervation, and multifactorial arrhythmogenesis.8–10 Each represents a potential objective for treatment. In addition, dynamic LV outflow tract (LVOT) obstruction is present in approximately 70% of HCM patients, either at rest or with physiological provocation. Left ventricular outflow tract obstruction is a major determinant of symptoms, such as dyspnoea, chest pain, or presyncope, and has represented the most visible and consistent target of therapeutic efforts in HCM (possibly with the exception of sudden death prevention), based both on drugs and invasive septal reduction strategies.11

Pharmacological interventions in patients with HCM are often necessary for control of limiting heart failure and anginal symptoms, LVOT obstruction, and arrhythmias.12 However, medical treatment strategies remain largely predicated on a small number of clinical studies, and are most often empirically based on personal experience or extrapolation from other cardiac conditions.13 Thus, although valuable clinical guidelines exist for HCM,1,2 the strength of recommendations for pharmacological treatment is largely not evidence based.
In recent years, the widespread use of imaging and genetic testing, coupled with an increasing awareness in the cardiology community, have led to the identification of large populations of individuals with HCM, regularly followed at international referral centres. At the same time, a number of genetic and pathophysiological studies have highlighted novel potential targets for disease-specific treatments. 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. Therefore, we believe it is timely to review the available evidence for pharmacological treatment of HCM, and highlight some of the relevant disease pathways which could be targeted by current or emerging drug therapies.

The evidence: a systematic review

Number and design of available studies
In a comprehensive Medline search (pubmed.gov), original articles, reviews, and editorials published in English were tracked, addressing the use of any pharmacological agent employed in HCM cohorts in the period 1950–2011, with the exception of case reports. References in each of the papers retrieved, as well as in HCM and heart failure guidelines, were also searched. A total of 45 studies were identified over the last 60 years (i.e. <1 per year), enrolling a total of 2121 HCM patients (Supplementary material online, Table S1). Study design in the majority of cases was prospective (n = 40, 87%); however, only 5 were randomized, double-blind placebo-controlled trials. The number of papers in a comparison of the period 1991–2011 vs. 1971–1990 demonstrated no increase in the number of studies (figure 1A), and only a modest increase in the number of patients enrolled (627 vs. 1473 patients, respectively). With regard to sample size, only 7 studies (15%) enrolled >50 patients, whereas 22 (49%) had <20 patients (Figure 1B). The maximum number of patients in a single prospective study was 118, in a disopyramide multicentre registry.

The majority of studies assessed β-blockers or calcium channel blockers (n = 36), while a smaller number focused on amiodarone (n = 5), disopyramide (n = 4), or a variety of other agents [angiotensin receptors blockers, propranolol, angiotensin-converting enzyme (ACE) inhibitors, perhexilline, and statins] (Figure 2). Thirty-nine studies were based on a single drug, and 6 assessed multiple drugs, including 4 studies with direct comparison of two agents (Supplementary material online, Table S2). The clinical endpoints assessed included non-invasive measurement of diastolic function (n = 13; 29%), relief of dynamic LVOT obstruction (n = 11; 25%), and prevention of arrhythmias and sudden death (n = 6; 13%) (Supplementary material online, Table S1). Of note, none of the studies has prospectively addressed the issue of the long-term outcome.

β-Adrenoceptor blockers

β-Blockers represent the mainstay of therapy and have proved effective in patients with angina or dyspnoea on effort, particularly when associated with LVOT obstruction, and are often employed to reduce the prevalence of non-sustained ventricular arrhythmias. These beneficial effects are mediated by sympathetic modulation of heart rate, ventricular contractility, and stiffness, leading to improved ventricular relaxation, increased time for diastolic filling, and reduced excitability. Despite these advantages, whether long-term treatment with β-blockers ultimately impacts outcome in HCM patients remains still undefined. Furthermore, it is unknown whether any specific agent is superior to the others, given the substantial dissimilarities of β-blockers with regard to pharmacodynamic profile, β-1 selectivity, metabolic interaction, and antiarrhythmic properties.

Five types of β-blockers have been used in 12 studies enrolling a total of 391 patients. Propranolol has been assessed in four early prospective studies focusing on acute gradient reduction and symptom relief in obstructive patients (Figure 3), and in one retrospective outcome study in a young HCM patient cohort. Furthermore, a double-blind placebo-controlled trial demonstrated symptomatic benefit with the use of nadolol over verapamil, whereas another, double-blind crossover trial showed sotalol to be effective in suppressing supraventricular and ventricular arrhythmias. Intriguingly, Melacini et al. in a retrospective evaluation reported that none of the patients on long-term treatment with sotalol in the Padua cohort experienced sudden cardiac death over a 7-year follow-up.

By virtue of their efficacy in reducing LVOT obstruction and myocardial ischaemia, current guidelines recommend β-blockers
Figure 2 Number of hypertrophic cardiomyopathy pharmacological studies (A) and number of patients enrolled (B), based on the type of drug employed. ACE-I, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Figure 3 Effects of beta-adrenergic blockade on subaortic obstruction. Simultaneous pressures recorded in the left ventricle (LV) and brachial artery (BA). Observations prior to the beta-adrenergic-blocking agent Nethalide are shown in the top three panels, while the observations following Nethalide administration are shown in the bottom three panels. Control measurements before exercise in each instance are on the left, measurements at the completion of the exercise period are in the centre, and after the cessation of exercise on the right. CO, cardiac output; AO, effective outflow orifice. The stippled area represents the LV–BA pressure gradient. Reproduced from Harrison et al.99
as first line agents in symptomatic patients, both with or without resting obstruction.2,12 With regard to inducible obstruction, two recent studies have consistently shown marked reduction or abolition in exercise-induced LVOT obstruction with bisoprolol at well-tolerated doses (S. Nistri, submitted for publication).23

Calcium channel blockers
Non-dihydropiridine calcium-channel blockers such as verapamil and diltiazem have been successfully employed in symptomatic patients with non-obstructive HCM. Conversely, HCM guidelines suggest caution in using calcium channel blockers in patients with significant LVOT obstruction, due to their potentially adverse haemodynamic effects.24–31 The beneficial effects of calcium channel blockers are largely mediated by their negative inotropic and chronotropic effects, leading to prolonged LV filling time and improved redistribution of flow towards the subendocardial layers of the LV.12,21,32 Verapamil is the single most studied agent in HCM, with 367 patients enrolled in 12 studies, of which 8 were single drug and 4 were multiple drug evaluations. Eight of these studies were prospective. To date, there is no definite evidence that verapamil effectively improves functional capacity in HCM, although the drug has been used for decades to ameliorate quality of life in non-obstructive patients, and is considered standard treatment.1,2,21,33–40 Diltiazem has been studied in 4 small prospective trials enrolling 55 HCM patients in total. In three, diltiazem was shown to improve LV diastolic parameters, either acutely or at mid-term administration, whereas one showed beneficial effects of the drug on myocardial ischaemia assessed by exercise-single photon emission computerized tomography (Supplementary material online, Table S1).41–44 Following intriguing pre-clinical evidence (reviewed below), an ongoing study is testing the hypothesis that diltiazem may prevent development of the HCM phenotype in genotype-positive individuals.45

Disopyramide
An old class I A antiarrhythmic drug, disopyramide has been used successfully to attenuate the pressure gradient and improve symptoms in patients with LVOT obstruction, generally in association with β-blockers.36–58 The beneficial effect of disopyramide is due to its negative inotropic action, reducing the drag forces that trigger dynamic subaortic obstruction. Its efficacy and safety have been demonstrated in a large retrospective registry.19 Nevertheless, concerns regarding QTc prolongation and significant anticholinergic side-effects may limit its long-term use. In our own practice, disopyramide is often used the short-term as a bridge to surgical myectomy in symptomatic patients with severe LV outflow obstruction.4

Amiodarone
Early data stimulated hopes that amiodarone might be highly protective in HCM, with regard to potentially malignant ventricular arrhythmias.50–53 However, its efficacy in preventing sudden death is now considered suboptimal, based on the fact that 20% of patients dying suddenly in one retrospective study were on active amiodarone treatment at the time of death.15 In addition, the well-known adverse side-effects of this drug render its long-term use challenging. At present, amiodarone remains the most effective and widely used treatment for atrial fibrillation (AF), although no study has specifically addressed such indication in HCM.50–53 In addition, the drug is often used for control of symptomatic ventricular ectopics, and to minimize the likelihood of appropriate discharge in patients with implantable defibrillators. To our knowledge, there is no systematic experience with dronedarone in HCM patients.

Other drugs
Very limited data exist regarding the use of angiotensin converting enzyme inhibitors in HCM. A relatively old study showed the acute effects of combined treatment of intracoronary enalapril and sublingual captopril in restoring coronary flow reserve.54 Four subsequent prospective randomized pilot trials suggested a potential benefit of renin–angiotensin–aldosterone (RAAS) inhibitors on LV function and progression of hypertrophy,55–57 but have not been followed by larger studies. In addition, Valsartan is effective in suppressing the synthesis of type I collagen in HCM patients, suggesting potential beneficial effects for prevention of myocardial fibrosis.58 A single study suggested a positive effect of intravenous propafenone in reducing LVOT obstruction.59 Finally, a pilot study enrolling 21 HCM patients, based on promising pre-clinical data, failed to prove significant modifications in echocardiographic indexes of LV hypertrophy following treatment with atorvastatin.60

Pharmacological control of left ventricular outflow tract obstruction
The pharmacological treatment of LVOT obstruction and related symptoms in HCM patients is based on a time-honoured combination of negative inotropic agents, including β-blockers, calcium antagonists, and disopyramide.1,2 In general, β-blockers are most effective on the latent, exercise-related form of LVOT obstruction, but tend to be less effective when severe obstruction is present at rest. Non-dihydropiridinic calcium antagonists such as verapamil or diltiazem are even less effective, because their negative inotropic action is partly counteracted by their gradient-enhancing vasodilating properties. Disopyramide has been proven safe and effective, but can be problematic in the long-term due to its anticholinergic side-effects and, in a significant percentage of patients, to a loss of clinical benefits decrease over time.7 As a result of these limitations, pharmacological control of symptoms in obstructive HCM patients is often less than optimal and may be poor. In the presence of drug refractory, disabling symptoms, invasive options such as surgical septal myectomy or, in a very selected subset of patients, septal alcohol ablation, represent the treatment of choice.61 Of note, obstructive HCM patients undergoing surgical myectomy have shown excellent long-term survival and reduced risk of sudden cardiac death compared with those treated conservatively with drugs.1,62

Management of atrial fibrillation
Atrial fibrillation is a common occurrence in HCM population, often representing a turning point in the clinical course by virtue of HCM-related mortality, symptomatic deterioration, and risk of stroke.12 The powerful independent association of AF with HCM-related mortality and morbidity underlines the necessity for aggressive therapeutic strategies in these patients,63 including early initiation of oral anticoagulation for the prevention of...
from other patient populations is extrapolated to HCM. Amiodarone is safe and effective in HCM patients, and is considered the drug of choice in most instances. Disopyramide has been shown to be safe when prescribed for control of LVOT obstruction, but its efficacy in prevention of recurrent AF is not well established. Furthermore, there are no data regarding the efficacy of other class I antiarrhythmic agents, sotalol, or dronedarone in HCM. Catheter-based ablation techniques have recently shown promising results in HCM patients with symptomatic AF refractory to medical treatment, but need to be assessed in larger cohorts and over longer follow-up periods.

Pre-clinical studies

We found nine experimental studies assessing pharmacological treatment in HCM animal models (Supplementary material online, Table S3). Long-term treatment with N-Acetylcycteine, a precursor to the most abundant intracellular non protein thiol pool against oxidative stress, reversed cardiac and myocyte hypertrophy and interstitial fibrosis, prevented LV systolic dysfunction, and improved arrhythmogenic propensity in an established transgenic rabbit model of human HCM. Resolution of cardiac and myocyte hypertrophy and prevention of cardiac systolic dysfunction with NAC are novel findings. The data suggest the potential beneficial effects of this drug in reversal of cardiac phenotype in HCM and prevention of global cardiac systolic dysfunction.

In a randomized placebo-controlled study in transgenic rabbits, the administration of atorvastatin prior to phenotypic expression prevented the development of cardiac hypertrophy over a 1-year period of observation. Prevention of cardiac hypertrophy was demonstrated at organ, cell, and molecular levels. Similar results were obtained by the administration of simvastatin. Furthermore, two randomized studies in mice and rats showed how RAAS antagonists, alone or in combination with aldosterone, were able to prevent and reverse myocardial fibrosis and hypertrophy, and two prospective studies demonstrated diltiazem to be effective in preventing development of hypertrophy and diastolic dysfunction in transgenic HCM mice. Finally, trimetazidine, a metabolic modulator with anti-Ca2+ properties, was effective in increasing survival and reducing heart and liver hypertrophy in cardiomyopathic Syrian hamsters.

Limitations of clinical trials in HCM

To date, the studies evaluating specific medical treatments for HCM have included little more than 2000 patients—i.e. a study sample less than a single, small multicentre heart failure, or coronary disease trial. The number of pharmacological studies per year has not increased over the last four decades, reflecting both difficulties and limited efforts directed at clinical research initiatives in this area. Most of these studies have employed surrogate endpoints such as exercise tolerance, change in LVOT gradients, or indexes of cardiac performance, and were therefore not powered to assess the impact of therapeutic interventions on the natural history and outcome of HCM. Thus, evidence-based approaches to novel treatments in HCM patients represent an urgent priority, emphasized by the recent report of the Working Group of the National Heart, Lung, and Blood Institute on ‘Research Priorities in Hypertrophic Cardiomyopathy’.

It is true that genetic cardiomyopathies pose a number of significant challenges with respect to designing and implementing properly powered, prospective randomized clinical trials. Hypertrophic cardiomyopathy is a relatively uncommon disease in which a limited number of patients are available for participation in randomized trials, even within the major international tertiary referral centres for this disease. Furthermore, in view of the relatively low event rates of hard cardiovascular endpoints associated with HCM, large populations are theoretically required in order to detect a benefit of any given treatment on prognosis. On the other hand, designing studies which incorporate ‘softer’ clinical endpoints, such as those based on non-invasive testing or serum biomarkers, is not optimal because they might represent a further hurdle to randomization.

Based on these considerations, for example, specific issues such as the long-term comparison of the survival benefits of surgical myectomy vs. alcohol septal ablation appear exceedingly difficult to address. On the other hand, the potential availability of integrated networks among international referral centres, several of which actively follow cohorts of >1000 HCM patients, might render the performance of these large trials possible. In selected subgroups, such as patients with evidence of adverse LV remodelling, at high risk of end-stage progression, pharmacological studies addressing outcome might be easier to perform, due to the substantially higher event rates expected.

While hard endpoints including total cardiovascular mortality, heart failure-related and sudden cardiac death remain the gold standard of any therapeutic investigation in HCM patients, it is reasonable to consider prospective studies incorporating more attainable but sound clinical endpoints, reflecting important features of the disease pathophysiology, which have previously been shown to have prognostic value. Specifically, advanced imaging techniques can be exploited to quantitate the effect of novel treatments on parameters such LV coronary microvascular function and myocardial tissue fibrosis. Clinical pilot studies designed with these endpoints might provide the rationale for the larger multicentre, international prospective studies necessary to determine, over a reasonable period of time, the benefit of novel treatments on the natural history of HCM.

Potential treatment targets

Plausible options for treatment of HCM patients include both novel indications of well-known drugs as well as the development of novel agents targeting disease-specific abnormalities. The latter approach, certainly the most promising, must necessarily derive from the clinical translation of advanced basic research. Therefore,
better understanding of the major mechanisms involved in HCM pathophysiology remains an essential pre-requisite for any ground-breaking advance in pharmacological treatment.\textsuperscript{14} (Figures 4 and 5).

**Aldosterone/angiotensin II and myocardial fibrosis**

In transgenic mouse models of HCM, aldosterone and angiotensin II (A-II) have been implicated in the pathogenesis of myocyte hypertrophy and disarray as well as increased interstitial fibrosis.\textsuperscript{71,78} In addition, myocardial aldosterone levels are increased up to fourfold in HCM patients compared with normal controls.\textsuperscript{79} These observations suggest that the RAAS feedback loop may be upregulated in HCM, similar to other chronic conditions where both A-II and aldosterone directly contribute to adverse cardiac and vascular remodelling. These changes ultimately lead to the promotion of myocardial fibrosis, a feature of HCM with relevant functional and prognostic implications.\textsuperscript{78} Further studies are needed to determine more

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**Figure 4** Disease pathways of hypertrophic cardiomyopathy, and potential therapeutic interventions. Various signalling pathways and disease mechanisms can be activated as the result of a specific gene mutation. (A) Disturbed biomechanical stress sensing. (B) Impaired calcium cycling and sensitivity. (C) Altered energy homeostasis. (D) Increased fibrosis. These pathways should not be considered in isolation because they can act in concert. LTCC, voltage-dependent L-type calcium channel; PLB, cardiac phospholamban; RyR2, ryanodine receptor 2; SERCA2, sarcoplasmic/endoplasmic reticulum calcium ATPase 2; SR, sarcoplasmic reticulum; TGF-\(\beta\), transforming growth factor \(\beta\); T-tubule, transverse tubule. Reproduced from Frey et al.\textsuperscript{92}
precisely the mechanisms responsible for local upregulation of these molecular mediators in HCM hearts. Nevertheless, experiments in rodent models of HCM have shown that drugs that inhibit aldosterone (e.g. spironolactone) or A-II (e.g. angiotensin II blockers) reduce myocardial fibrosis, attenuate the extent of myocyte disarray, and improve diastolic function. These observations have led to human HCM cross-sectional studies demonstrating that serum markers of collagen synthesis are increased over degradation and related to diastolic function. At present, the clinical efficacy of anti-remodelling drugs in HCM is uncertain. However, evidence derived from patients with other forms of heart disease such as hypertensive cardiomyopathy in which there are structural abnormalities of the intramural arterioles and patterns of fibrosis similar to HCM support a potential beneficial effect of these drugs on coronary microvascular remodelling, fibrosis, and diastolic function. Greater insight in this area will hopefully be gained following the completion of an on-going single-centre randomized, double-blind, placebo-controlled trial exploring whether mineral corticoid receptor blockade reduce myocardial fibrosis in HCM patients [Martin Maron, MD, oral communication]. The primary endpoint of this study is the effect of spironolactone on serial measurements of serum markers of collagen synthesis.

Figure 5 Physiopathology of myocardial ischaemia in hypertrophic cardiomyopathy.
and degradation at baseline and 12 months follow-up. Promising applications of aldosterone/A-II inhibition include prevention of development of the HCM phenotype in genotype-positive individuals, and prevention to end-stage progression in patients with adverse LV remodelling and declining cardiac function.\textsuperscript{14}

**Cascade of myocardial ischaemia**

Myocardial ischaemia due to severe coronary microvascular dysfunction is a well-established pathophysiologic feature of HCM\textsuperscript{81} (Figure 5). Marked structural abnormalities of the small intramural coronary arteries, including medial hypertrophy, intimal hyperplasia, and decreased luminal size, are considered the most relevant substrate producing microvascular dysfunction and myocardial ischaemia in HCM. Microvascular ischaemia appears to occur more frequently in patients with evidence of sarcomere myofilament mutations (Figure 6).\textsuperscript{82} Additional features such as myocyte disarray, interstitial fibrosis, and reduced capillary density may contribute to the impairment of tissue perfusion.\textsuperscript{83}

Severe coronary microvascular dysfunction is a strong, independent predictor of clinical deterioration and death.\textsuperscript{84,85}
Microvascular dysfunction is often present in patients with only mild or no symptoms and can precede clinical deterioration by years. Thus, the pathophysiologic cascade of events, leading from remodelling and dysfunction of the intramural coronary arterioles to myocardial ischaemia and replacement fibrosis, is an ideal therapeutic target (Figure 5).

There is no proven treatment capable of improving coronary microvascular function in HCM. However, the anatomic and functional features of coronary microvascular remodelling in HCM are very similar to those described in hypertensive cardiomyopathy. Mourad et al. carried out a pilot study using PET to investigate the effects on the coronary microcirculation of 6 months of antihypertensive treatment with a very low-dose combination of the ACE inhibitor, perindopril, and the diuretic, indapamide. The study results suggest that treatment with this drug combination can improve coronary microvascular function in hypertensive patients. A subsequent PET study by Neglia et al. confirmed the results in hypertensive patients. In addition, in an ancillary study, these authors demonstrated, in a well-established animal model of LV hypertrophy (the spontaneously hypertensive rat—SHR) that the effects of perindopril plus indapamide on myocardial blood flow are due to reverse remodelling of coronary arterioles and reduction in vessel rarefaction.

Other drugs, with different mechanisms of action, have the potential to improve coronary microvascular function in HCM. Some of these drugs act on the extravascular component of coronary resistance by improving diastolic relaxation (ranolazine) or prolonging filling of the coronary reservoir by prolonging diastole (ivabradine). Others, such as the activators of soluble guanylate cyclase (cGMP), might provide additional, direct anti-remodelling effect on the microvasculature. Based on recent genetic and molecular insights, further studies are needed to address novel pharmacological approaches to microvascular dysfunction in HCM.

**Deranged intracellular energy utilization**

Hypertrophic cardiomyopathy is characterized by abnormal cardiomyocyte energetics, as reflected by a reduced phosphocreatine/ATP ratio, measured by means of magnetic resonance spectroscopy, both in animal models and in patients. Inefficient energy handling and energy depletion are believed to represent a cause of hypertrophy in HCM. Thus, agent improving the energetic profile of cardiomyocytes are now available, which hold promise in targeting the intracellular pathways of hypertrophy and dysfunction in HCM. This important study provides a rationale for further consideration of metabolic therapies in HCM.

**Late sodium current and calcium handling abnormalities**

Hypertrophic cardiomyopathy is associated with a complex electrophysiological cardiomyocyte remodelling involving multiple changes in transmembrane currents. Enhanced late sodium current has recently been described in isolated cardiomyocytes from HCM patients, causing intracellular calcium (Ca$^{2+}$) overload and ultimately leading to abnormal energy handling and increased arrhythmogenicity. Selective late sodium current inhibition by ranolazine markedly improved these abnormalities in vitro. Thus, ranolazine represents a promising therapeutic option in HCM patients, with potential benefits similar or even greater than those described in patients with coronary artery disease.

A multicentre, double-blind, placebo-controlled pilot study is currently underway to test the efficacy of ranolazine on exercise tolerance and diastolic function in symptomatic HCM patients (EUDRA-CT 2011-004507-20).

In addition, studies on HCM patients and animal models have highlighted several direct consequences of sarcomere gene mutations on intracellular calcium handling, pointing to SERCA2a, phospholamban, and related proteins as promising therapeutic targets. A strategy currently under scrutiny is based on the observation that inhibition of plasma membrane L-type Ca$^{2+}$ channels by diltiazem normalizes aberrant levels of Ca$^{2+}$ and prevents fibrosis and cardiac dysfunction in mouse models of HCM. Consequently, an ongoing trial is evaluating the effect of prophylactic treatment with diltiazem in genotype–positive hypertrophy-negative HCM patients, with the aim of preventing the development of LV hypertrophy (NCT00319982).

**Conclusions**

Five decades following the original description of HCM, there is still a dismal paucity of data supporting pharmacological treatment strategies for this complex disease. By comparison, device-based, percutaneous, and surgical treatments of LVOT obstruction have received significantly greater attention, although rarely in a double-blind randomized fashion. This can be regarded as a paradox, as only a minority of patients requires surgery or a device, whereas the large majority is treated pharmacologically. Of all the potential new targets for pharmacological treatment, three seem to be closer to fruition, i.e. cardiomyocyte electrophysiological and metabolic dysfunction, coronary microvascular dysfunction, and increased interstitial fibrosis.

Drugs capable of improving the metabolic efficiency of the cardiomyocyte are now available, which hold promise in targeting the intracellular pathways of hypertrophy and dysfunction in HCM hearts. Coronary microvascular dysfunction can lead to myocardial ischaemia and replacement fibrosis in HCM, resulting in adverse LV remodelling and dysfunction. Likewise, increased interstitial fibrosis appear to derive from an upregulated RAAS feedback loop, similar to other chronic conditions where both A-II and aldosterone directly contribute to adverse cardiac and vascular remodelling. Pilot, proof of principle studies are in the process to be started to ascertain if established drugs, proven effective in other conditions, may lead to reversal of this phenomenon in HCM.

In the next future, as our understanding of the pathophysiology of HCM increases, the availability of transgenic models of the disease, functional imaging techniques, and genome-wide analysis capabilities will hopefully provide clues to novel and promising treatment modalities for HCM. However, these will only remain
hypotheses until systematic clinical evidence can be systematically obtained from adequately designed clinical trials. The changing epidemiology of the disease now allows what was previously impossible: it is high time to move HCM into the era of evidence-based management.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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**Conflict of interest**

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**References**


