

## **Hypertrophic Cardiomyopathy: The Far And The Near**

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## 1 **Abstract**

2 Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disorder,  
3 affecting 1 in 500 of the general population. Existing studies may have underestimated its  
4 prevalence, however, owing to limited inclusion of individuals with early, incomplete phenotypic  
5 expression. Morbidity may result from diastolic dysfunction, left ventricular outflow tract  
6 obstruction, ischaemia, atrial fibrillation, abnormal vascular responses and, in 5%, progression to  
7 the "burnt out" phase with systolic impairment. Most of the disease-related mortality is due to  
8 sudden cardiac death, followed by heart failure, and embolic stroke. A majority of individuals with  
9 HCM, however, can look forward to normal or near-normal life expectancy, thanks in part to  
10 contemporary management strategies including family screening, risk stratification,  
11 thromboembolic prophylaxis, and implantation of cardioverter-defibrillators. The clinical  
12 guidelines for HCM issued by the American College of Cardiology Foundation/American Heart  
13 Association and European Society of Cardiology facilitate evaluation and management. This  
14 review aims to assist clinicians in navigating those guidelines, highlighting differences between  
15 them, key updates, current gaps in the knowledge base, and challenges in implementation -  
16 including aids and pitfalls in clinical and pathological evaluation. Also covered are the advances in  
17 genetics, imaging, and molecular science that will underpin future developments in diagnosis and  
18 therapy, both the far and the near.

19

## 20 **Introduction**

21 Stepping back and viewing hypertrophic cardiomyopathy (HCM) from a **chronological** perspective  
22 reveals many reasons for optimism. **In contemporary series of HCM cases from adolescence**  
23 **through adulthood, disease-related mortality is estimated at 0.5%/year, comparable to that in the**  
24 **general population, with over 60% of survivors reporting normal exertional capacity (NYHA class**  
25 **I) 1, 2.** In children the evaluation of both morbidity and mortality is complicated by the impact of  
26 aetiology on disease course. After excluding inborn errors of metabolism, malformation syndromes,

1 and neuromuscular disorders, however, children with HCM who survived infancy had an annual  
2 mortality of 1% 3.

3

4 Such favourable outcomes contrast starkly with accounts of HCM from half a century ago. Of the  
5 eight cases in Donald Teare's now-classic description of asymmetric hypertrophy of the  
6 interventricular septum, seven had died suddenly under the age of 45 4. The French-Canadian  
7 family in whom the hereditary basis of HCM was established, and the first causal mutation  
8 identified, had suffered recurrent losses to both cerebrovascular accidents (CVA) and SCD 5. In  
9 tertiary centre HCM cohorts from the late 1970s and early 1980s, the annual death rate was as high  
10 as 2-4%/ year in adults and 4.2-5.9% in children 2, 3, 6, -8.

11

12 At least part of the reason for the apparent declines in morbidity and mortality from HCM is  
13 awareness of and adjustment for the selection bias inherent in tertiary centre studies. Debilitating  
14 symptoms are significantly less prevalent among HCM cases at regional centres than at referral  
15 units (4% vs. 44% in one study) 9. In HCM cases ascertained between 1981-2002, from both a  
16 regional and a referral centre cohort of whom 25% were identified through family screening - both  
17 measures intended to limit selection bias - the annual disease-related mortality was 1.3-1.4% 10,  
18 11. These estimates remain, however, almost three-fold higher than those from contemporary  
19 studies, suggesting that other factors are also at play 1, 2. Chief among them is the advent of both  
20 modern external and implantable cardioverter-defibrillators (ICDs); the annual incidence of  
21 resuscitated out-of-hospital cardiac arrest and ICD discharge for ventricular tachyarrhythmia was,  
22 respectively, 0.6% and 0.9% in a recent series of younger HCM cases (mean age 20±5) 2. The  
23 advent of the ICD has been justifiably hailed as a game-changer in the prevention of SCD among  
24 at-risk individuals, selection of whom is facilitated by the availability of evidence-based algorithms  
25 for risk stratification in HCM.

1 Not all ICD discharges in individuals with nonischaemic heart disease represent a reliable surrogate  
2 for SCD, however, particularly when interventions for ventricular tachycardia are included in the  
3 endpoint 12. The improvements in survival and quality of life may owe as much to development of  
4 reliable imaging and rhythm monitoring; timely diagnosis of index cases; identification of  
5 phenotypic mimics, with implications for management; prospective evaluation of relatives, aided in  
6 some families by genetic analysis; the ability to link dyspnoea, angina, and other common  
7 symptoms to underlying causes such as diastolic dysfunction, left ventricular outflow tract  
8 obstruction (LVOTO), and ischaemia; availability of safe and effective pharmacotherapy for most  
9 complications (Table 1); honing of techniques for invasive septal reduction in drug-refractory  
10 LVOTO; and framing of consensus guidelines that have standardised evaluation and rationalized  
11 the myriad available treatment options 13, -18.

12

13 Also not to be discounted are the impact of simple measures, such as early detection of atrial  
14 fibrillation (Afib) to enable prophylactic anticoagulation, and discouraging individuals with a  
15 confirmed diagnosis of HCM from engaging in competitive sports. The latter may represent the  
16 single most common lifestyle advice offered to individuals with HCM; supportive evidence comes  
17 indirectly from the Italian pre-participation screening programme, which has been associated with  
18 an 89% decline in the incidence of SCD among athletes 19. There has been no concomitant change  
19 in the incidence of SCD in the unscreened nonathletic population, and no deaths among the athletes  
20 diagnosed with HCM, pointing to a potential benefit from sports disqualification *per se*. From a  
21 distant and objective vantage point, then, considerable progress has been made in the  
22 understanding, evaluation, and management of HCM.

23

#### 24 **Contemporary Challenges in HCM**

25 Conversely, individuals with HCM may feel there is little room for complacency. They have been  
26 labelled, often at a relatively young age, with a diagnosis that has implications for obtaining

1 mortgages and life insurance and requires lifelong follow-up. The disease will at worst result in  
2 SCD, stroke, or progressive heart failure and at best remain stable, but there is no prospect of  
3 remission. No cure currently exists and the available treatment options - ranging from drug therapy  
4 to septal reduction and device implantation - are not without possible side effects or complications.  
5 To cap it all, HCM is predominantly inherited in an autosomal dominant fashion, which translates  
6 into a 50% probability of having transmitted the causal mutation to any children.

7

8 The challenge of determining risk/ benefit ratios for any form of treatment is only too familiar to  
9 healthcare providers, who have the additional burden of uncertainties about evaluation, diagnosis,  
10 and surveillance of patients with HCM. The comprehensive clinical guidelines for HCM issued by  
11 the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and  
12 European Society of Cardiology (ESC) arm frontline clinicians to make informed decisions, but a  
13 panacea they are not 14, 15. Policy makers, health service chiefs, and subspecialty experts harbour  
14 concerns about heterogeneous implementation of the guidelines; the accessibility and quality of  
15 imaging and ancillary investigations, particularly at non-referral units; and whether sufficient  
16 clinical experience and support systems such as genetic counselling are available in primary/  
17 secondary care settings.

18

19 Gaps in both knowledge and understanding of HCM also continue to loom large. Owing to the  
20 paucity of randomised clinical trials and large scale studies, most recommendations are based on  
21 consensus opinion of experts, small scale and retrospective studies, and/or registries; on a handful  
22 of key issues, sufficient data upon which to base clinical decisions are still awaited 14, 15. There is  
23 detailed advice, for example, on differentiating HCM from LV hypertrophy (LVH) secondary to  
24 hypertension or athletic adaptation, but interpretation of the requisite investigations in African-  
25 Caribbean individuals continues to pose difficulties, as does the distinction of late-onset HCM from  
26 isolated basal septal hypertrophy in the elderly. Nowhere is the dearth of knowledge more apparent,

1 however, than in the management of relatives with subclinical/ incomplete phenotypic expression,  
2 increasingly identified by sophisticated imaging techniques and mutation screening.

3  
4 Previously the exclusive preserve of highly selected families attending referral units with research  
5 laboratories, genetic testing has now been pushed to the forefront of the clinical arena by rapid  
6 advances in genotyping technology and large genomic repositories, which have also provided a  
7 powerful platform for genetics research. Despite simultaneous progress in bioinformatics, a  
8 bottleneck has arisen in the analysis and interpretation of the vast quantities of raw complex data  
9 produced. Already, however, gene variants previously presumed pathogenic are being recast as  
10 benign or modifying, and vice versa 20. Lagging further behind is the translational research needed  
11 to integrate the new genetic discoveries into clinical practice.

### 13 **Objectives**

14 Instead of reiterating the ACCF/ AHA (2011) and ESC (2014) guidelines for HCM, we aim to  
15 assist providers in navigating them by surveying the main points of divergence, key updates,  
16 unresolved issues, and challenges in implementation - including aids and pitfalls in diagnosis. We  
17 also discuss the impact of advances in genetics and imaging on early diagnosis. Briefly highlighted  
18 are ongoing efforts to elucidate the molecular mechanisms underpinning the disease, which hold  
19 promise of substrate-modulating therapy in the not-too-distant future.

### 21 **Controversies in the Definition of HCM**

22 HCM is a heritable disorder of the heart muscle with a well described clinical-pathological-genetic  
23 profile. Recognised clinical manifestations include diastolic dysfunction, LVOTO (Figure 1), mitral  
24 regurgitation, inappropriate vasodilation during exertion, microvascular ischemia, Afib, ventricular  
25 arrhythmia, SCD, and - less commonly - progression to a "burnt out" stage with wall thinning,  
26 cavity dilation, and impairment of systolic function, sometimes accompanied by moderate-to-

1 severe pulmonary hypertension (Table 1) 13, -1821. Typical findings on pathology are LVH,  
2 myocyte disarray, small vessel disease, and both replacement and interstitial fibrosis 22. Among  
3 HCM cases of known aetiology, mutations in genes encoding components of the sarcomere - the  
4 contractile apparatus of the cell - predominate in every age-group beyond infancy. Most commonly  
5 implicated are the thick-filament genes, beta-myosin heavy chain (*MYH7*) and myosin binding  
6 protein C (*MYBPC3*), but a sizeable minority also harbour defects in thin-filament genes, including  
7 cardiac troponin T (*TNNT2*) and I (*TNNI3*),  $\alpha$ -tropomyosin (*TPMI*), and cardiac actin (*ACTC*).  
8 None of these features, however, is pathognomonic of HCM and no universally accepted definition  
9 for the disease therefore exists.

10

11 The ACCF/AHA and ESC definitions for HCM overlap considerably but differ in breadth.  
12 According to the ACCF/AHA, HCM is a disease state characterized by unexplained LVH  
13 associated with nondilated ventricular chambers in the absence of another cardiac or systemic  
14 disease that itself would be capable of producing the magnitude of hypertrophy evident in a given  
15 patient, with the caveat that patients who are genotype positive may be phenotypically negative  
16 without overt hypertrophy 14. The ESC defines HCM as the presence of increased LV wall  
17 thickness that is not solely explained by abnormal loading conditions 15. Both definitions, it should  
18 be noted, are based on the presence of LVH, although this stipulation is not without its drawbacks;  
19 both also exclude hypertrophy due to pressure or volume overload, while allowing for possible  
20 coexistence of pressure/ volume overload states with HCM.

21

## 22 *Phenotypic Mimics of Sarcomeric HCM*

23 LVH resembling archetypal sarcomeric HCM also occurs in a number of other disease states,  
24 accounting for an estimated 5% of adult and a still higher proportion of childhood cases 15. The  
25 oft-used designation of "phenocopy" refers specifically to an environmentally determined disease  
26 state that mimics a heritable disorder. In common parlance, however, the term phenocopy is also

1 widely applied to genetic disorders with cardiac phenotypes akin to HCM (strictly, "genocopies").  
2 Whether pheno- and genocopies are best classified within the spectrum of HCM is a point of  
3 contention between current guidelines; from the European perspective, they are, at the very least to  
4 promote awareness among clinicians of their existence; by the narrower American definition, they  
5 are not, a position justified in part by major differences from sarcomeric HCM. Semantics aside,  
6 however, timely recognition of phenotypic mimics is important because of the distinctive clinical  
7 profiles, natural histories, therapeutic options, and inheritance patterns (Table 2) 15, 23, -38.

#### 9 *Limitations of LVH-based definition*

10 One shortcoming shared by both the ESC and ACCF/AHA definitions of HCM is the stipulation of  
11 LVH for a diagnosis of HCM. The American version allows for genotype-positive phenotype-  
12 negative individuals without hypertrophy, but not for the existence of a phenotype without  
13 hypertrophy 14, 15.

14  
15 One of the best documented examples of disease expression without LVH was originally observed  
16 on post-mortem examination of four SCD victims from the same family. The hearts appeared  
17 macroscopically normal, with weights, cavity size, and wall thickness within reference ranges;  
18 histology, however, revealed widespread myocardial disarray 39. A mutation in thin-filament gene  
19 *TNNT2* was subsequently identified in the family, including a surviving relative in whom  
20 echocardiography was unremarkable, but 12-lead ECG and blood pressure response to exercise  
21 were abnormal 40. A further post-mortem series affirmed the occurrence of sudden premature death  
22 in individuals with *TNNT2* mutations and severe myocyte disarray, minimal LVH and fibrosis  
23 notwithstanding 41.

24  
25 A fuller picture emerged from a study of 71 adults and 21 children ( $\leq 16$  years) with *TNNT2*  
26 mutations from 20 families. Of the adults, 76% had abnormalities on echocardiography and all



1 arrhythmic events occurred in individuals with 15-27 mm of LVH. In contrast, echocardiography  
2 was normal in 90% of the children, of whom 1 suffered SCD despite LV wall thickness of only  
3 9mm. Besides a family history of SCD, the most common risk predictor was an abnormal blood  
4 pressure response to exercise, which was observed in 48% of adults and 40% of children, and may  
5 precede the appearance of LVH 42. A subsequent study found that maximal wall thickness (MWT)  
6 was lower and LVOTO less prevalent among unrelated index cases with thin (n=80) vs thick  
7 (n=150) filament mutations, whereas systolic dysfunction, restrictive LV filling, and progression to  
8 NYHA class III/IV were significantly more common; there was no difference in the incidence of  
9 arrhythmic events 43. Taken together, available data argue against increased arrhythmic risk in thin  
10 filament disease, but suggest that expression of LVH is milder and age-dependent; SCD in its  
11 absence is uncommon but recognised; and extensive myocyte disarray is the most likely substrate  
12 40, -43.

13  
14 The question then arises as to whether the defining feature of HCM should be not LVH but the  
15 histological hallmark of myocyte disarray, which has also been documented in non-sarcomeric  
16 variants including Anderson-Fabry disease, Noonan's syndrome, and Friedreich's ataxia, but not  
17 *PRKAG2* mutations 44, -46. Myocyte disarray is more widespread in the hearts of individuals who  
18 had an abnormal blood pressure response to exercise, features of ischaemia (chest pain, marked ST  
19 depression on exercise testing, and/or perfusion defects), or died suddenly 47. Lacking, however, is  
20 a direct clinical surrogate for myocyte disarray and the consequent inability to assess its presence or  
21 extent *in vivo* represents the chief downside to a definition based on histology.

22  
23 Defining HCM on its genetic basis, as a disease of the sarcomere, has the dual advantages of being  
24 readily testable and encompassing otherwise subclinical disease forms. The prevalence of  
25 sarcomeric mutations among both adults and children with HCM varies from 40-60%, depending,  
26 among other factors, on the panel of genes screened and the study population 15. Also implicated in

1 HCM are accessory and related proteins in the sarcomere (e.g., myosin light chain kinase 2 and  
2 phospholamban), albeit in a minority of cases, all of whom could arguably fall under this diagnostic  
3 umbrella [15](#). Outside its scope, as in the US guidelines, are the 5-10% of HCM cases with pheno-  
4 or genocopies, which may be justifiable on the grounds of distinct disease profiles [14, 15](#). Less  
5 justifiable from a clinical standpoint is the exclusion of the residual 25-30% of HCM cases with  
6 archetypal disease but no detectable mutation in the known disease-causing genes [15](#).

7  
8 Another argument against genetic definition is the lack of specificity; the same defects in *TNNI3*  
9 underlie both HCM and restrictive cardiomyopathy in some families ([Figure 2](#)), while other  
10 sarcomeric mutations have been implicated in dilated cardiomyopathy [48, -51](#). One proposed  
11 alternative is mechanistic definition, which shifts the putative final common pathway of HCM from  
12 the sarcomere to primary cellular energy depletion, thereby offering a unifying therapeutic target  
13 [52](#). The fundamental premise, however, has not yet gained widespread acceptance.

### 15 **Challenges in the Evaluation of HCM**

16 Clinicians, imaging specialists, and geneticists alike are confronted by a number of challenges in  
17 the evaluation of HCM. The diagnosis is not always straightforward even on pathology,  
18 notwithstanding the ability to examine the whole heart at both a macroscopic and microscopic level  
19 ([Box 1](#)) [22](#). Experience aids in avoiding the common pitfalls, some of which are discussed below,  
20 but uncertainties persist in a few key areas - such as differentiation of HCM from isolated basal  
21 septal hypertrophy and interpretation of genetic variants of unknown significance - owing to an  
22 incomplete knowledge base. [14, 15](#).

#### 24 *Clinical Work-up for HCM*

25 [The preliminary work-up for an individual with suspected HCM includes obtaining a clinical](#)  
26 [history, compiling a pedigree, physical examination, 12-lead ECG, and imaging, typically two](#)

1 dimensional (2D) echocardiography. Maximal upright exercise testing and rhythm monitoring are  
2 indicated in confirmed cases to provide prognostic information; they may also shed light on the  
3 aetiology of symptoms (Table 3) 13, 15, 51.

4  
5 Echocardiography has an incontrovertible niche in the assessment of valve structure and function  
6 and latent LVOTO. Despite the natural bias against replacing trusted modalities, slow  
7 implementation of new technologies, and delays in developing standardised protocols and  
8 measurements, however, cardiovascular magnetic resonance (CMR) is increasingly recognised as a  
9 valuable complement to echocardiography in the evaluation of HCM. Besides not being limited by  
10 acoustic windows, CMR offers high spatial resolution and non-invasive, *in vivo* tissue  
11 characterisation, with a number of accepted (Table 3) and emerging indications (Box 2; Figures 3-  
12 4) 15, 53, -68.

#### 13 14 *Limitations of Contemporary Diagnostic Criteria and Practice*

15 CMR has recently confirmed what cardiac pathologists have long known: any degree and  
16 distribution of LVH may be consistent with HCM (Figure 2) 22, 68. Yet current diagnostic criteria  
17 for HCM in adult index cases still hinge on the presence, in one or more LV myocardial segments,  
18 of LV end-diastolic wall thickness  $\geq 15$ mm 14, 15 - without adjustment for age, sex, or body surface  
19 area. Nor are normal regional variations in LV wall thickness taken into account; consequently, the  
20 diagnostic threshold varies from 2-6 standard deviations above the normal adult mean depending  
21 on the segment under scrutiny 69. The exclusive focus on maximal wall thickness (MWT) and  
22 reliance on cut-offs are a throwback to the M-mode era, when the full phenotypic spectrum awaited  
23 elucidation and the diagnostic capabilities of imaging were limited.

24  
25 Best viewed as one integral component of the diagnostic and prognostic profile of HCM, the MWT  
26 requires careful measurement at multiple different levels. Outside of referral centres, it is not

1 uncommon for the MWT measurement to have been made at the basal level only, or to have  
2 incorporated false tendons or right ventricular structures.

3  
4 Both the ACCF/AHA and ESC guidelines recommend that diagnosis of HCM in children be based  
5 on LV wall thickness >2 standard deviations above the mean for age, sex, and body size - a  
6 necessary advance over unindexed cut-offs 14, 15. The paediatric criteria have nevertheless come  
7 under criticism for achieving increased sensitivity at the potential expense of specificity; the grey  
8 area separating physiological and pathological LVH is purported to fall between 2-3 standard  
9 deviations over the population mean 70. As in adults, the presence of other abnormalities on ECG  
10 and echocardiography (e.g., diastolic dysfunction) facilitate differentiation of load-induced LVH  
11 from HCM. Additional considerations in children are presented in Box 3 3, 8, 35, 71, -77.

### 12 13 *Diastolic Function Assessment*

14 Much variation also exists in the quality of diastolic function assessment, although the ESC  
15 guidelines for HCM recommend that this should be comprehensive and include Doppler  
16 myocardial imaging, pulmonary vein flow velocities, pulmonary artery systolic pressure, and  
17 measurement of left atrial (LA) size 15. Not only is diastolic dysfunction one of the main causes of  
18 dyspnoea and exertional limitation in HCM, but it also serves as a risk predictor. In a study of 239  
19 consecutive HCM cases, a restrictive LV filling pattern (ratio of mitral peak velocity of early filling  
20 (E) to mitral peak velocity of late filling (A)  $\geq 2$ ; E-wave deceleration time  $\leq 130$  ms) was an  
21 independent marker of increased risk of HCM-related death or transplantation (hazard ratio (HR)  
22 3.54, 95% confidence interval [CI] 1.91-6.57,  $p < 0.001$ ) 78.

### 23 24 *Estimation of LA Dimensions*

25 Also of value as a prognostic aid in HCM is quantification of LA size. The most reproducible linear  
26 measurement is the anteroposterior LA diameter, which has been extensively used in

1 echocardiography practice and as a clinical marker. Because LA remodelling may not affect all  
2 dimensions to the same extent, however, there has been a recent push towards estimation of LA  
3 volumes, which have the edge in terms of accuracy and show stronger clinical associations 79, 80.  
4 The 2015 consensus guidelines for cardiac chamber quantification by echocardiography  
5 recommend 2D measurement of LA volume using the disk summation algorithm, followed by  
6 indexing to body surface area 81. The reproducibility of indexed LA volume in a real-world setting  
7 is not well established and as a relative recent adoption, it is not available for large-scale  
8 retrospective studies. As such, the LA diameter remains the parameter of choice in many studies,  
9 including two recent multi-centre investigations into factors influencing the risk of  
10 thromboembolism and SCD in HCM 82, 83.

11

12 As might be expected, the LA diameter is increased in HCM cases with Afib (45.4mm [CI 41.6-  
13 49.0]) vs sinus rhythm (38.0mm [CI 34.6-41.4]) 84. CMR based evaluation of LA remodelling in  
14 HCM has further identified LA ejection fraction (<38%), LA end-diastolic volume ( $\geq 118$ ml), and  
15 age ( $\geq 40$  years) as independent predictors of Afib 85.

16

17 LA diameter has also shown to be an independent predictor of thromboembolism (HR 1.03 [CI  
18 1.01–1.05]) in a multivariate analysis of 4,821 HCM cases with and without Afib over 10 years of  
19 follow-up. There was a positive linear relationship between LA diameter and the 5-year risk of  
20 thromboembolism up to ~45-50mm, at which point it became exponential. Among HCM cases with  
21 sinus rhythm at baseline and LA diameter >50mm, the annual incidence of thromboembolism  
22 (CVA, transient ischaemic attack, or systemic peripheral embolus) was 0.47% 82. While further  
23 investigation into the risk/ benefits of anticoagulation in this subgroup is awaited, frequent and  
24 perhaps prolonged ambulatory ECG monitoring is warranted, as the burden of silent paroxysmal  
25 Afib may be significant.

26

1 Other independent predictors of thromboembolism in the HCM cohort as a whole included age (HR  
2 1.03 [CI 1.02-1.04], Afib (HR 8.41 [CI 1.95-36.35], prior thromboembolism (HR 3.63 [CI 1.81-  
3 7.29]), NYHA class III/IV (HR 2.07 [CI 1.81-7.29]), and MWT (HR 1.45 [CI 1.12-1.88]). In  
4 contrast, the CHA2DS2-VASc score appears to have low predictive accuracy in HCM and use is  
5 not recommended in this population; an alternative model for predicting the absolute 5-year risk of  
6 thromboembolism for an individual with HCM has been proposed (HCM Risk-CVA) [82](#).

7  
8 The predictive utility of LA remodelling also extends beyond Afib and thromboembolism. In both  
9 Italian and American HCM cohorts, LA diameter >48 mm has been shown to be independently  
10 associated with a twofold increase in the risk of cardiovascular death after adjustment for age, sex,  
11 resting LVOTO, and Afib [86](#). The 2014 European model for SCD risk prediction in HCM (HCM  
12 Risk-SCD) includes LA diameter as one of its component markers [83](#).

#### 13 14 *Limitations of LV Ejection Fraction*

15 Longitudinal contractile function in HCM is commonly and consistently reduced, both globally and  
16 regionally, coincident to the sites of hypertrophy. Evaluation of circumferential and radial function  
17 has produced discrepant results, with both reduction and compensatory enhancement reported [87](#), -  
18 [89](#). Even when all components of strain (longitudinal, transverse, circumferential, and radial) are  
19 depressed, however, the LV ejection fraction often appears normal or increased, giving the false  
20 impression of "good" systolic function. The reason for this discrepancy has recently become  
21 apparent from mathematical modelling of LV contraction. The LV ejection fraction has two  
22 determinants, viz., myocardial shortening (strain) and end-diastolic wall thickness; when the latter  
23 increases, so does radial wall thickening. Consequently, the presence of LVH leads to  
24 overestimation of LV systolic function. A nomogram with corrected LV ejection fractions for  
25 different LV wall thicknesses is now available, but awaits validation in the clinical setting [90](#).

26

1 *Pitfalls in the Assessment of LVOTO*

2 Besides being a major cause of symptoms, LVOTO ( $\geq 30$  mm Hg) at rest is an independent  
3 predictor of HCM-related death (relative risk 1.6 [1.1-2.4]), and hence routinely sought during the  
4 initial diagnostic echocardiogram 91. Also recommended is image acquisition while the subject  
5 performs the Valsalva manoeuvre in sitting, semi-reclining and - if necessary - standing positions,  
6 although the prognostic impact of provokable obstruction remains unresolved. In the absence of a  
7 haemodynamically significant ( $\geq 50$  mm Hg) resting or provokable LVOT gradient, the US  
8 guidelines advise proceeding to exercise stress echocardiography to identify latent obstruction 14.  
9 The European approach, in contrast, is dependent on whether the individual has symptoms of  
10 LVOTO (e.g., dyspnoea, chest pain, exertional limitation and/or impaired consciousness); if  
11 present, exercise stress echocardiography is warranted. For asymptomatic individuals, further  
12 investigation for latent LVOTO is not considered necessary unless "relevant to lifestyle advice and  
13 decisions on medical treatment." 15

14

15 In a study of 201 HCM cases with gradients  $< 50$  mm Hg at rest, 76 (38%) developed gradients  $\geq 50$   
16 mm Hg after exercise, lending support to routine stress echocardiography 92. Conversely, there is a  
17 paucity of evidence to suggest that latent LVOTO is an adverse prognostic indicator. As such, there  
18 may be little to be gained from instituting treatment in asymptomatic cases.

19

20 Obstacles to implementing the recommendations on exercise stress echocardiography at most  
21 centres include the lack of suitable facilities and staff with the requisite training and experience.  
22 This is true even of many tertiary referral units without a special interest in inherited cardiovascular  
23 disease. Consequently, pharmacological provocation with dobutamine and nitrates remain in  
24 widespread use, although they do not resemble physiological stressors; dobutamine is poorly  
25 tolerated, prone to yielding false positives, and best avoided; nitrate use should be reserved for  
26 individuals unable to perform an exercise test 15.

1

2 Doppler echocardiography for LVOTO, particularly during exercise studies, may be fraught with  
3 problems, most of which can be avoided by awareness and experience (Box 4, Figure 5) 93, -96.

4

#### 5 *Impact of High Throughput Techniques on Genetic Diagnosis*

6 Both the ESC and AHA/ACCF guidelines recommend offering genetic testing to individuals with a  
7 confirmed clinical diagnosis of HCM, largely because identification of a causal variant enables  
8 cascade screening of relatives, thereby affording lifelong reassurance to the ~50% who are not  
9 carriers 14, 15. The yield may be up to 60% in HCM, while in the remaining cases the result is  
10 either indeterminate (no suspicious variant found) or uncertain, owing to identification of a variant  
11 of unknown significance. The pivotal challenge is determining whether an isolated sequence  
12 variant is pathogenic from multiple lines of evidence, including: *in silico* models; *in vitro*  
13 functional and expression studies; co-segregation with clinical status in an affected family;  
14 alteration of an evolutionarily conserved amino acid residue; and absence/ rarity among healthy  
15 control subjects.

16

17 Enter massively parallel sequencing techniques, which are estimated to have reduced cost and  
18 enhanced throughput by more than threefold, leading to rising clinical demand for genetic testing.

19 At the same time, growing public awareness of heritable disease through media coverage has  
20 increased uptake. At least part of the clinical need is met by commercial outsourcing, with many  
21 independent facilities also offering fee-based direct-to-consumer services. Screening is  
22 accomplished via large chips enriched for  $\geq 50$ -200 cardiac genes or more ambitious "fishing  
23 expeditions" with whole-exome or whole-genome sequencing 97. These high-output approaches  
24 are proving a double-edged sword, however, by providing extensive coverage of implicated genes  
25 and plausible candidates on the one hand, while uncovering numerous sequence variants requiring  
26 bioinformatic and clinical interpretation on the other. The response to this challenge has been



1 pragmatic, entailing a shift to probabilistic classification of variants ("pathogenic," "likely  
2 pathogenic," "uncertain significance," "likely benign," and "benign", according to  
3 recommendations), coupled with a receptiveness to reclassification as more information emerges  
4 20, 97. The latter is of particular importance in relatives undergoing predictive testing and is best  
5 broached during pre-test counselling. Index cases consenting to whole-exome sequencing with a  
6 view to new gene discovery should be warned of the likelihood of incidental findings, such as  
7 detection of a familial cancer gene with uncertain clinical implications 97.

8  
9 The bulk of the findings from high-throughput genotyping in HCM have been in line with those  
10 obtained from Sanger sequencing. Missense variants predominate (>75%), with small insertions/  
11 deletions accounting for most of the remainder 98. Copy-number variants, defined as genomic  
12 deletions and duplications greater than 1 Kb, have been investigated for the first time and appear to  
13 be present in <1% of HCM cases, consistent with low tolerance of the sarcomeric genes to variation  
14 99, 100. The pick-up rate is otherwise similar; in a study of 223 unrelated HCM cases, 131 (59%)  
15 had rare variants of likely or confirmed pathogenicity in sarcomeric, calcium-handling, and Z-disc  
16 genes (excluding titin), with most hits detected in *MYBPC3* and *MYH7*, followed by *TNNT2* and  
17 *TNNI3* 101. An overlapping subgroup of 96 cases (43%) had non-synonymous variants in  
18 desmosomal and ion channel genes, mostly of unknown significance; the frequencies were,  
19 however, not significantly different from those observed in the control population. *RYR2*, *CAV3*,  
20 and *SCN5A* have previously been implicated in HCM, but the possibility now arises that their role  
21 is modifying rather than pathogenic 101.

22  
23 Perhaps the most striking example of genetic interaction in HCM is the gene-dose effect observed  
24 in cases with 2 (compound/ double heterozygous or homozygous) or 3 sarcomeric mutations, who  
25 respectively comprise ~5% and ~0.8% of reported series 102, 103. Multiple "hits" may predispose  
26 to earlier age at onset, greater septal wall thickness, and increased risk of arrhythmic events and

1 progression to burnt-out disease [102, -104](#). Identification of a single pathogenic variant in an index  
2 case does not, therefore, obviate the need to screen the rest of the panel of HCM-related genes.  
3 Specific examples of non-sarcomeric modifiers in HCM include "pro-LVH" renin-angiotensin-  
4 aldosterone (RAAS) gene variants, which are associated with increased manifestation and severity  
5 of LVH and, in children, with progressive LVOTO [105, 106](#). The prevalence of severe LVH  
6 (MWT $\geq$ 30 mm) appears significantly higher among HCM cases with rare variants in *ANK2* [107](#).  
7 Variants in calcium handling genes may also influence the expression and age of onset of LVH [98](#),  
8 [108](#). Most of these purported modifying associations await further investigation in independent  
9 studies.

10

11 The ratio of published to novel variants in one of the high-throughput sequencing studies was 1:1, a  
12 departure from the abundant private mutations previously reported in HCM, with the latter quite  
13 possibly an overestimate [101, 102](#). An excess of private mutations in a genetically determined  
14 disease is usually contingent upon a high rate of spontaneous mutations, coupled with frequent pre-  
15 reproductive death, which prevents them from perpetuating in the gene pool. Neither is true of  
16 HCM, in which *de novo* mutations are recognised, but only ~15% of cases are sporadic and  
17 premature death is fortunately not common [102](#). It is more likely that the prevalence of HCM-  
18 related variants in the general population has been underestimated; sequencing of 8 sarcomeric  
19 genes in 3,600 individuals from the Framingham and Jackson Heart study cohorts identified 1 or  
20 more probably pathogenic variant in 0.6% (>1 in 200) [109, 110](#). As genomic repositories grow,  
21 more apparently private mutations may be reclassified as rare.

22

23 [Although at least 1 in 200 of the general population may be carriers of pathogenic sarcomeric gene](#)  
24 [variants, estimates of the prevalence of HCM tend to cluster around 1 in 500, suggesting either](#)  
25 [gene variants of markedly reduced penetrance and expressivity, or clinical under-diagnosis of the](#)  
26 [disease \[109, 110\]\(#\)](#). The reality is likely a combination of the two; most of the original prevalence

1 studies enrolled unrelated adults only, or employed a diagnostic criterion of MWT $\geq$ 15mm, or both,  
2 thereby resulting in under-recognition of early, familial disease 110.

3

#### 4 **Challenges in the Diagnosis of HCM**

##### 5 *Prospective Evaluation of Families*

6 Among 90 carriers of HCM-related mutations, the proportion fulfilling conventional diagnostic  
7 criteria increased with age, being 55% in the 10-29 year age group, 75% between 30 and 49 years,  
8 and 95% over the age of 50 111. Because the pre-test probability is higher in relatives, however, the  
9 diagnostic threshold is set lower, at  $\geq$ 13 mm in one or more LV myocardial segments 15. Delayed  
10 onset (age $>$ 40) is nevertheless recognised in Troponin T and myosin essential light chain disease  
11 and is particularly prominent among myosin binding protein C mutation carriers, a proportion of  
12 whom have maximal wall thickness  $<$ 13mm beyond the age of 60 112, -114.

13

14 Age-related expression underpins consensus recommendations for lifelong surveillance of  
15 genetically affected individuals, which is typically commenced at  $\sim$ 10-12 years of age because  
16 clinical manifestations often develop during the pubertal growth spurt 14, 15. Serial clinical  
17 evaluation with 12-lead ECG and imaging is performed annually (6 monthly if borderline features  
18 are present) until physical maturity is attained, and every 5 years thereafter through adulthood. In  
19 the  $\sim$ 40% of families in whom no pathogenic mutation can be identified, the first-degree relatives  
20 of clinically affected cases should be offered surveillance on the basis that they are genotype-  
21 positive until proven otherwise.

22

23 Opinions differ as to whether children under the age of 10 should undergo either clinical screening  
24 or predictive genetic testing, with the ESC guidelines advising to the contrary, except in the  
25 presence of family history of early-onset disease, symptoms, or exposure to highly strenuous  
26 physical activity 15. The views of the parents are also worth taking into account. Another grey area

1 is whether clinical screening in families of unknown genetic status should extend to second-degree  
2 relatives, who for practical reasons are often overlooked, but may have inherited the trait from a  
3 parent with nonpenetrant disease.

4  
5 There is a pressing need for characterisation of early phenotypic features in HCM to monitor  
6 disease development in gene carriers and facilitate screening of families without an identifiable  
7 mutation. Prior efforts to do so focused on integrating mild morphological abnormalities identified  
8 on echocardiography with 12-lead ECG features, culminating in the 1997 criteria for familial HCM  
9 (Table 4), long used in specialist centres to standardise diagnosis in relatives 115. Since then,  
10 advances in imaging technology and biomarker analysis have elucidated the spectrum of early  
11 disease still further (Box 5 Figure 6) 116, -127. Whether prognostic assessment is indicated in  
12 genotype-positive/ LVH-negative individuals should be decided on a case-by-case basis, pending  
13 long-term observational studies to establish their clinical course and outcomes. Available data  
14 suggest that abnormal blood pressure response to exercise and diastolic dysfunction may precede  
15 the development of LVH, but their prognostic impact in this subgroup is not clear 40, 42, 115, 116.

#### 16 17 *Isolated Basal Septal Hypertrophy (Sigmoid Septum)*

18 Isolated hypertrophy of the basal septum, also known as sigmoid septum, becomes more common  
19 with increasing age, reaching 7.8% over 70 years 128. Reports suggest either an equal sex ratio or  
20 increased prevalence in women 128, 129. The clinical background often includes hypertension.

21 Clinical manifestations include exertional limitation, chest pain, and dyspnoea inadequately  
22 unexplained by LV systolic dysfunction or coronary artery disease. Both diastolic dysfunction and  
23 systolic anterior motion of the mitral valve, resulting in dynamic LVOTO, have been implicated,  
24 with clinical improvement on beta-blockers and disopyramide 128, 129. Generally absent,  
25 however, are the prolonged mitral valve leaflets and papillary muscle abnormalities recognised in  
26 HCM 128. The presence of LV outflow obstruction in this subgroup appears to be related not to the

1 maximum wall thickness, but to hypercontractile LV function and the position of the mitral valve  
2 leaflets with respect to the LV outflow tract 128.

3

4 Among 181 individuals with isolated basal septal hypertrophy who underwent screening of 8  
5 HCM-related sarcomeric genes, causal mutations were isolated in only 15 (8%), considerably less  
6 than the usual pick-up rate 130. This suggests that a small proportion of individuals with isolated  
7 hypertrophy of the basal septum have HCM (possibly late-onset or late-presenting). A distinct  
8 pathogenic mechanism is presumably at work in the remainder; there are a number of physiological  
9 reasons why the basal septum might be especially prone to hypertrophic response. That the  
10 aetiology is often difficult to establish has little influence on management of the individual, but  
11 poses the dilemma of whether to offer screening to blood relatives. Genetic analysis may facilitate  
12 identification of the minority with HCM, but a negative result does not exclude the disease.  
13 Awaiting identification are clinical features that would enable distinction between HCM and non-  
14 heritable isolated basal septal hypertrophy. There is a knowledge gap here, acknowledged in the  
15 ESC guidelines, which recommend that the decision be based partly on the presence of symptoms  
16 in family members 15.

17

### 18 *Individuals of African Descent*

19 In most racial groups, maximal wall thickness  $\geq 15$ mm and repolarisation abnormalities on the 12-  
20 lead ECG distinguish HCM from load-induced LVH. In contrast, individuals of African-Caribbean  
21 descent appear to have increased propensity towards LVH and repolarisation changes at relatively  
22 low levels of cardiovascular stress, be it hypertension or athletic training. Coupled with ethnic  
23 variations in the normal ECG and echocardiogram, this poses a major challenge in evaluating  
24 African-Caribbean individuals for inherited cardiovascular disease. For African-Caribbeans with a  
25 background of hypertension, for example, the ESC guidelines advocate raising the diagnostic  
26 threshold for coexisting HCM to MWT  $\geq 20$ mm 15. At the same time, HCM may be under-

1 recognised among African-Caribbeans; in one US series, African Americans accounted for 55% of  
2 competitive athletes who died suddenly with a post-mortem diagnosis of HCM, but only 8% of  
3 clinically identified HCM cases [131](#).

4  
5 Cardiac evaluation of both athletes and healthy, non-athletic control subjects of African ancestry  
6 has established many clinical features as benign. Among them are increased LV trabeculation, ST  
7 segment elevation with upward domed convexity, and inverted T-waves in V1-4, which are  
8 prevalent among African-Caribbean individuals regardless of their sports participation history [15](#),  
9 [132](#), [133](#). Findings are less clear-cut with respect to lateral T-wave inversion, which is considerably  
10 less prevalent (2.4-4.1% of African-Caribbean athletes and 0.7-3.4% of controls) and was present  
11 in two athletes who were subsequently diagnosed with HCM, one of whom suffered aborted  
12 cardiac arrest. Conversely, resolution of inferolateral T-wave inversion has also been observed in  
13 African-Caribbean athletes following periods of detraining [132](#), [133](#). Large, long-term follow-up  
14 studies are awaited to further define the significance of this pattern among those of African  
15 ancestry.

## 17 **Controversies in Management**

### 18 *Controversies in Risk Stratification*

19 Prior cardiac arrest or sustained ventricular tachycardia is an unequivocal indication for ICD  
20 therapy for secondary prevention [14](#), [15](#). All other individuals with a confirmed clinical diagnosis  
21 of HCM, be they index cases or relatives, should be offered non-invasive prognostic assessment at  
22 baseline and follow-up (typically annually) because of the unpredictable and sometimes  
23 progressive disease course [14](#), [15](#). The 2003 joint ACC/ESC consensus document on HCM  
24 amalgamated evidence from a host of studies identifying predictors for SCD to propose a unifying  
25 algorithm ([Figure 7](#)) [13](#), [134](#). This was widely and successfully adopted into clinical practice, albeit  
26 with considerable heterogeneity in the interpretation of the risk factors; a family history of SCD, for

1 example, was variously qualified to deaths below the age of 40 or to deaths among first-degree  
2 relatives only 135. As its limitations became evident, however, a number of amendments were  
3 proposed, with the upshot that the 2011 ACCF/AHA and 2014 ESC guidelines now differ  
4 conspicuously in their approach to prognostication 14, 15.

5  
6 The threshold for intervention was revisited in a study of 506 HCM cases with ICDs, which found  
7 no difference in the likelihood of appropriate discharge between recipients with 1, 2, or 3 of the  
8 predictors evaluated. Omitted from the risk profile were an abnormal blood pressure response to  
9 exercise, ancillary markers such as ischaemia and LVOTO and, in 74 cases (19%), ambulatory  
10 ECG monitoring data 136. Despite these drawbacks, the apparent presence of a single risk factor in  
11 more than a third of ICD recipients with appropriate interventions provided much of the impetus  
12 for subsequent revision of the U.S. recommendations. The 2011 ACCF/AHA guidelines upgraded 3  
13 factors to class IIa (reasonable) indications for ICD therapy, while still recognising the others as  
14 risk- predicting or modifying in combination (Figure 7) 14.

15  
16 A validation study incorporating all 5 principal risk factors was subsequently conducted in 1,606  
17 HCM cases followed up for a median of 6.6 years 137. Consistent with an additive effect, the  
18 cumulative incidence of SCD/ appropriate ICD discharge was significantly higher among cases  
19 with  $\geq 2$  vs no risk factors (HR 3.3, 95% CI 1.94 to 5.75,  $p < 0.001$ ), although not in cases with 1 vs  
20 no risk factors (HR 1.4, 95% CI 0.82 to 2.51,  $p = 0.212$ ). Nevertheless, the original algorithm fell  
21 short on the following counts. First, of the 660 cases with no risk factors, 20 (3%) suffered events  
22 (annual rate 0.45%, 95% CI 0.29 to 0.70), a devastating if infrequent occurrence that precludes  
23 affording complete reassurance to any patient. Second, the positive predictive value for events was  
24 relatively low (22.4% for  $\geq 2$  risk factors), resulting in a sizeable proportion of patients being  
25 exposed to the risks of device implantation without tangible benefit. Third, the original algorithm  
26 assigned the 636 cases with one risk factor to an intermediate risk stratum, with an annual event

1 rate of 0.65%. Fourth, the area under the receiver operating characteristic curve (C-statistic) for  
2 prediction of arrhythmic events was 0.64 at 5 years, indicating limited power to discriminate high  
3 from low risk individuals 137.

4

5 The novel SCD risk model now endorsed by the ESC was developed from a multicentre,  
6 retrospective, longitudinal cohort study of 3675 HCM cases with a view to providing individualised  
7 5-year risk estimates 83. Putative risk factors were eligible only if identified from multivariate  
8 analysis, resulting in exclusion of abnormal blood pressure response to exercise, upgrading of  
9 maximal LVOT gradient at rest or during Valsalva, and two new additions, viz., LA diameter and  
10 age. The model predicts that for every 16 ICDs implanted in HCM cases with  $\geq 4\%$  5-year SCD  
11 risk, one individual will be saved from SCD at 5 years 83. Independent validation studies have  
12 yielded mixed results, but most data suggest HCM-Risk-SCD outperforms both previous  
13 prognostication strategies. In a tertiary centre cohort of 706 HCM cases without prior events, the C-  
14 statistics for the 2003 algorithm, 2011 ACCF/AHA guidelines, and HCM-Risk-SCD were 0.55,  
15 0.60, and 0.69, respectively 138. In a Spanish study of 48 HCM cases with ICDs, HCM-Risk-SCD  
16 was the only factor independently associated with the onset of ventricular tachyarrhythmia (OR  
17 1.46, CI 1.05-2.01) and none of the 11 cases with low risk estimates suffered events 139. A U.S.  
18 report of 1,629 HCM cases has proved the exception so far, with 21/35 (60%) of SCD/ cardiac  
19 arrest victims apparently having risk estimates of  $< 4\%$ /5 years, although few details of the  
20 prognostic assessment were supplied 140.

21

22 Inherent criticisms of HCM-Risk-SCD include limited applicability to children and those with  
23 phenotypic mimics of archetypal HCM, in whom validation data are currently lacking; absence of  
24 any assessment of the prognostic role of latent LVOTO; failure to factor in the prognostic benefits  
25 of therapeutic measures including invasive septal reduction, beta-blockers, and amiodarone; and  
26 exclusion of ancillary predictors such as ischaemia 15, 83, 141. The most significant omission was



1 an abnormal blood pressure response to exercise, which has a 95% negative predictive value and is  
2 one of the most important factors for risk stratifying individuals with minimal or severe LVH 40,  
3 42, 142. None of these drawbacks, however, need impact adversely on patient care, since the model  
4 does not seek to abrogate clinical experience or judgment. The achievement of HCM-Risk-SCD  
5 lies in the shift from relative to absolute risk estimation, which is more meaningful for the  
6 individual; future refinements will improve its generalisability and performance, pending more data  
7 from intensive phenotyping and prospective validation studies.

### 8 9 *New and Unresolved Issues in the Management of LVOTO*

10 By international consensus, both septal myectomy and catheter-based transcatheter alcohol septal  
11 ablation (Box 6) are best performed by experienced operators in the setting of a dedicated  
12 programme 14, 15, 143, -160. Recent data affirm that high procedural volume may be associated  
13 with 3-4 lower rates of in-hospital deaths and complications, from septal myectomy in particular  
14 144, 145. HCM cases are considered candidates for invasive septal reduction in the presence of (1)  
15 resting or provoked LVOT gradient  $\geq 50$  mmHg; (2) sufficient anterior septal thickness (typically  
16  $>16$ mm); and (3) either NYHA class III/IV limitation or exertional syncope/ near-syncope, despite  
17 maximum tolerated pharmacological therapy 14, 15, 134, 143. Growing confidence in the net  
18 benefit of invasive septal reduction therapy at specialist HCM units has led to calls for more  
19 latitude in the eligibility criteria, so that the choice might be available to select cases with NYHA  
20 class II symptoms following full discussion of the risks involved 161.

21  
22 In children, septal myectomy is the recommended procedure because of its track record of efficacy,  
23 safety, and favourable long term outcomes, although the small aortic annulus makes exposure  
24 more difficult and increases the risk of aortic (5.5%) or mitral (1.5%) valve injury 14, 15, 162, 163.  
25 Recurrent obstruction is also more common in the paediatric population owing to ventricular  
26 remodelling 164.

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In adults, the European guidelines do not rank either option as superior to the other, but advocate pre-interventional assessment of all patients by a multidisciplinary team to facilitate selection. In contrast, the ACCF/AHA position favours ventricular septal myectomy as first-line, reserving alcohol septal ablation for patients who are either at high operative risk or wish to avoid surgery 14, 15. At least part of the justification for this preference may be reports of septal myectomy as an independent predictor of (1) disease-related survival among HCM cases with LVOTO and (2) time to appropriate discharge among HCM cases with ICDs, with both gradient relief and substrate reduction have been invoked as possible explanations 141, 165, 166. Furthermore, concerns persist regarding the arrhythmogenic potential of the scar generated by alcohol ablation, with at least one study identifying alcohol septal ablation as independently associated with arrhythmic events (HR 5.2, CI 1.2-22.1 vs myectomy cases) - a key reason why the procedure is usually avoided in children 134, 167. To date, however, most meta-analyses of alcohol septal ablation vs. myectomy have found it non-inferior in terms of subsequent functional improvement, short- and long-term mortality and - in one instance - superior with respect to SCD (OR 0.32 CI 0.11-0.97) 151, 168, - 170.

In HCM cases with significant drug-refractory LVOTO but relatively mild LVH ( $\leq 16$  mm), neither septal myectomy nor alcohol septal ablation is typically suitable owing to increased risk of iatrogenic ventricular septal defect. Dual chamber pacing is one option; also underway are trials of biventricular pacing for LVOTO (NCT01332162, NCT01614717), after pilot studies yielded promising results (Box 6) 14, 15, 151, -160. The alternative is to shift attention from the thickened septum to the abnormalities of the mitral valve/ papillary muscles that predispose to systolic anterior motion (Figure 1), and for which both conventional surgical and newer, catheter-based interventions are available 21, 171, 172. One example of the latter is the MitraClip, which has been successfully used to shift the residual anterior leaflet edge away from the LVOT by combining it

1 with the posterior leaflet (A2 to P2) in a handful of cases 173. Innovations in the surgical  
2 management of LVOTO include minimally-invasive, robot-assisted myectomy in which access to  
3 the septum is obtained via left atriotomy and through the mitral valve 174, 175.

#### 4 5 *Antibiotic Prophylaxis for Endocarditis*

6 Damaged/ abnormal native heart valves and any part of the endocardium disrupted by turbulent  
7 blood flow can become a nidus for bacterial seeding and consequent infective endocarditis. As a  
8 complication of HCM, infective endocarditis has been observed almost exclusively in cases with  
9 LVOTO (gradient  $\geq 30$  mm), in whom the annual incidence is estimated to be 0.38%, increasing to  
10 0.92% in the presence of coexisting LA dilation ( $\geq 50$  mm) 176. Precipitants such as recent dental  
11 work or other procedure were identified in 4/10 cases in one series; none had received coincident  
12 antibiotics. Although no longer mandated by guidelines, the benefits of endocarditis prophylaxis  
13 may outweigh the minimal risks of antibiotic administration in this subgroup 177.

#### 14 15 **Frontiers of Therapy**

##### 16 *New Strategies for Old*

17 The past decade has seen a number of therapies introduced and integrated into general cardiology  
18 practice and accepted in some settings as standard of care. Approval of these therapies for use in  
19 subspecialty practice is often won more slowly because their safety and efficacy in subpopulations  
20 such as inherited cardiovascular disease patients have not been established.

21  
22 Examples include the direct-acting oral anticoagulants that selectively inhibit factor Xa  
23 (rivaroxaban, apixaban and edoxaban) and thrombin (dabigatran). The ESC guidelines advocate  
24 they be used in HCM patients when vitamin K antagonists cannot, owing to side effects, inability to  
25 perform INR monitoring, or failure to maintain therapeutic anticoagulation 15. Dabigatran receives

1 mention in the ACCF/AHA guidelines as a non-inferior alternative to vitamin K antagonists for  
2 thromboprophylaxis in Afib, with the caveat that data in HCM cases are not available 14.

3

4 Catheter ablation for Afib has not only grown almost exponentially in popularity, but is also  
5 increasingly considered a first-line treatment for a subgroup of patients in general cardiology  
6 practice. Meta-analyses suggest a complication rate in HCM cases comparable to that in the general  
7 population, offset by a greater need for repeat procedures and anti-arrhythmic drugs to prevent Afib  
8 recurrence. Putative predictors of relapse following ablation include LA remodelling and diastolic  
9 dysfunction, with conflicting data on LVOTO 178, 179. Criteria for selecting the HCM patients  
10 most likely to benefit from Afib ablation are awaited.

11

12 Subcutaneous ICDs hold particular appeal for individuals with HCM, many of whom will have  
13 devices *in situ* for decades and otherwise incur concomitantly prolonged exposure to the risk of  
14 lead-related complications. Although most HCM cases having no pacing requirement, estimates  
15 vary as to the proportion who satisfy the additional prerequisite of suitable vectors on surface ECG  
16 screening. Eligibility rates of 84-93% have been reported, being higher when right parasternal leads  
17 are tested and lower among high-risk patients 180, 181. High T-wave voltages appear to be the  
18 main cause of screening failure, consistent with an increased prevalence of inappropriate shocks  
19 due to T-wave oversensing among HCM patients with subcutaneous devices 181, -183. Proposed  
20 solutions include careful monitoring of device recipients, exercise testing during screening and  
21 follow-up, and fine-tuning of the discrimination algorithm, perhaps by adding a 2.5 mm/mV gain  
22 setting 180, -182.

23

24 *Towards Substrate-modulating Therapy*

25 Because they can worsen haemodynamics, the consensus advice is to avoid renin-angiotensin  
26 system inhibitors and other vasodilators in HCM cases with resting or latent LVOTO; their role is

1 currently limited to the "burnt out" phase, which is characterised by systolic dysfunction and  
2 managed with conventional heart failure therapy 14, 15, 92. There has been some interest in  
3 whether renin-angiotensin system inhibitors might exert a disease-modifying effect on LVH and  
4 fibrosis earlier in the course of nonobstructive HCM. A pilot study (n=20) of losartan vs placebo  
5 was promising, reporting a significantly larger increase in the extent of late gadolinium  
6 enhancement in the placebo group after 12 months. The subsequent randomised controlled trial  
7 INHERIT (n=133), however, found no significant differences in left ventricular mass, global  
8 longitudinal strain, Doppler measures of diastolic function, or LA volume between the losartan and  
9 placebo groups after the same time period 18, 184, -186. Recruitment is ongoing for the VANISH  
10 trial (NCT01912534), which will evaluate the safety and efficacy of valsartan in preventing disease  
11 progression still earlier in the natural history of HCM: among mutation carriers, both LVH-negative  
12 and positive (NYHA class I-II).

13  
14 Currently in development are approaches to substrate modification ranging from metabolic  
15 modulators to small molecule effectors and gene therapies for "rescuing" HCM at the level of the  
16 biomechanical defect. The myocyte action potential, calcium handling, sarcomeric function, and  
17 energy utilisation (Figure 8-9) serve as the primary targets 18, 52, 187, -196.

18  
19 The action potential of a typical cardiac myocyte is shown in Figure 8. Laboratory studies of  
20 cardiomyocytes from HCM cases undergoing septal myectomy have demonstrated  
21 electrophysiological abnormalities including prolonged action potential duration and increases in  
22 the late  $\text{Na}^+$  and  $\text{Ca}^{2+}$  currents, diastolic  $\text{Ca}^{2+}$  concentration, and the occurrence of early and  
23 delayed afterdepolarisations 187, 188. The late sodium current inhibitor ranolazine - better known  
24 as an anti-anginal drug - partially reversed these effects *in vitro*, reducing arrhythmogenicity and  
25 improving diastolic function in ventricular trabeculae 187, 188. Results are awaited from  
26 RESTYLE-HCM, a double-blind placebo-controlled study of the effect of ranolazine on exercise

1 capacity in symptomatic HCM cases; a similar trial, LIBERTY-HCM, of the new selective late  
2 sodium current inhibitor eleclazine is ongoing (NCT02291237) 18.

3  
4 One popular school of thought holds that HCM-related mutations sensitise the myofilaments to  
5 calcium - shifting the force-pCa curve to the left (Figure 9C, red line) - and augment the overall  
6 power output of the cardiac muscle, resulting in hypercontractility and impaired relaxation 189,  
7 190. Putative therapeutic targets include *TNNI3* which, when phosphorylated at residues S23 and  
8 S24 by protein kinase A, desensitises myofilaments to  $Ca^{2+}$ . Reducing the phospholamban/  
9 SERCA2a ratio, by inducing suppression of phospholamban or overexpression of SERCA2a, has  
10 the potential to shorten relaxation times and improve diastolic function 190.

11  
12 The defective sarcomere is also purported to trap excess calcium ions, preventing normal  $Ca^{2+}$   
13 recycling; the corollary is depletion of calcium stores in the sarcoplasmic reticulum, accompanied  
14 by reduced expression of calsequestrin and RyR2 191. In an animal model of HCM, early  
15 administration of diltiazem not only restored normal levels of sarcoplasmic reticular proteins, but  
16 also forestalled development of LV hypertrophy, myocyte disarray, and fibrosis 191. By blocking  
17 L-type  $Ca^{2+}$  channels, diltiazem may persistently diminish calcium-induced calcium release,  
18 thereby limiting calcium retention within the mutant sarcomere and impeding an apparently critical  
19 event in the histopathological progression of HCM 191. The clinical applicability of these findings  
20 has been evaluated in a pilot, double-blind trial of diltiazem vs placebo in LVH-negative carriers of  
21 sarcomeric mutations over a 3-year treatment period 192. There were significant differences  
22 between the treatment and placebo arms in echocardiographic MWT, CMR LV mass index, and  
23 E/E' among carriers of mutations in *MYBPC3* (n=12) but not *MYH7* (n=21) 192.

24  
25 The variable efficacy of drugs affecting myocardial calcium handling may be down to the fact that  
26 a proportion of HCM mutations demonstrate the reverse pattern: desensitizing the system to

1 calcium - with a rightward shift of the force-pCa curve (Figure 8C4, blue line) - and/or attenuating  
2 the overall power output 193. Nor does the genetic locus offer any guide to functional impact;  
3 different mutations in *MYH7*, for example, demonstrate opposing effects on myofilament calcium  
4 sensitivity and contractility 193. For any given mutation, however, the properties of the affected  
5 myocardium can be elucidated anew and treatment tailored accordingly. Pending the advent of  
6 reliable *in silico* models, this can be accomplished through *in vitro* studies.

7

8 Motility assays typically are performed using purified recombinant sarcomeric protein constructs  
9 containing the mutation under investigation 194. Depicted in Figure 9B is a single-molecule dual-  
10 beam optical trap that allows direct measurement of the parameters determining the ensemble force  
11 (upper equation), velocity (lower equation), and hence the power output (graph) of the sarcomere  
12 189, 194. Small molecule modulators can then be designed to counteract the effects of the  
13 mutation. Strategies to modify ensemble force generation include (1) altering the affinity of the  
14 interaction of MYBPC3 with its binding site(s) on myosin. If more myosin heads are functionally  
15 inhibited by MYBPC3, there will be fewer available to interact with actin ( $N_t$ ), and vice versa; and  
16 (2) changing the pace of the weak to strong transition, which will impact on the total cycle time ( $t_c$ ),  
17 and hence the duty ratio ( $t_s/t_c$ ) 189, 197. A promising example of the latter is myosin-ATPase  
18 inhibitor MYK-461, which reduces the rate of phosphate release without slowing ADP release,  
19 thereby increasing  $t_c$  without increasing  $t_s$ , leading to a decrease in the duty ratio  $t_s/t_c$ , and reduction  
20 in both ensemble force and power 198. In mice with hypercontractile mutations in the myosin  
21 heavy chain, early chronic administration of MYK-461 prevented the development of LVH,  
22 myocyte disarray, and fibrosis, and normalised expression of profibrotic and mitochondrial (energy  
23 utilisation) genes 198. Preliminary data from Phase 1 clinical trials indicate that MYK-461 is well  
24 tolerated with dose-dependent pharmacokinetics (<http://www.myokardia.com/>).

25

1 Force-pCa relations have also been investigated at the molecular level using the 3-bead optical trap  
2 assay and a mini-ensemble of myosin heads, but additional insights into the pathogenesis of HCM  
3 have been gained from studies of single muscle fibres **193**. The latter are most readily sourced from  
4 slow-twitch skeletal muscle fibres, which express sarcomeric mutations and have the added  
5 advantages of being easily biopsied and less prone to the adaptive responses observed in  
6 myocardium (Figure 9C1-4) **193**. The summary graph (C4) confirms that sensitising and  
7 desensitising HCM mutations shift the average force-pCa relation to the left and right, respectively.  
8 Apparent from the experimental plots, however, is one aberration shared by both mutated muscle  
9 samples: a wider spread among the constituent curves - indicating greater divergence in the  
10 behaviour of individual fibres - than wild-type. This may be attributable to the range in proportions  
11 of mutant mRNA found in individual muscle fibres (10-100%) and, indeed, individual  
12 cardiomyocytes **193, 195**.

13  
14 Assuming the observed functional variation between mutated cardiomyocytes and muscle fibres is  
15 true for HCM in general, it may represent the final common pathway of disease expression **195**.  
16 Uneven force generation in a branching cellular network leads to imbalances in contraction, stretch,  
17 and relaxation, which lead to transient and ultimately chronic structural distortion, viz., myocyte  
18 disarray **195**. Inefficient ATP usage is another probable corollary, tying in with the energy  
19 depletion hypothesis (Figure 9D) **52**. Increased expression of trophic factors ensues, with  
20 development of hypertrophy and interstitial fibrosis; **accumulating evidence points to oxidative**  
21 **stress as an exacerbating factor** **52, 195**. This paradigm has at least twofold consequences for  
22 therapy. First, generic treatments that exert the same effect on all cardiomyocytes are liable to have  
23 limited efficacy. Second, the need to target specific mutations (with, for example, small molecule  
24 effectors) or a unifying mechanism (such as energy depletion **or oxidative load**) is underscored **195**.

25



1 One of the first efforts to correct the myocardial energy deficit was a randomised controlled trial of  
2 the metabolic modulator perhexiline vs. placebo in 46 participants with HCM 199. The treatment  
3 group showed significant improvements in peak oxygen consumption during exercise, NYHA  
4 class, diastolic function, and myocardial ratios of phosphocreatine to ATP (a marker of cardiac  
5 energetic status) as measured by <sup>31</sup>P magnetic resonance spectroscopy 199. Perhexiline is a  
6 carnitine palmitoyl-acyltransferase inhibitor that shifts mitochondrial metabolism from fatty acid to  
7 carbohydrate utilisation, leading to oxygen sparing and enhanced myocardial efficiency; adverse  
8 effects associated with long-term use include hepatitis and peripheral neuropathy, but - as with  
9 amiodarone - the risk can be minimised by maintaining plasma concentrations within the  
10 therapeutic margin 200. A Phase 3 trial of perhexiline in 350 participants with moderate-to-severe  
11 HCM was announced in 2015 (NCT02431221).

12  
13 Administration of the antioxidant glutathione precursor N-acetylcysteine (NAC) to animal models  
14 of HCM is reported to have normalised the oxidised to total glutathione ratio and the levels of  
15 glutathiolated myofilaments and reversed increased myofailment Ca<sup>2+</sup> sensitivity, hypertrophy,  
16 interstitial fibrosis, and diastolic dysfunction 201, 202. Still in Phase 1, but also aimed at  
17 individuals with overt HCM, is the ongoing HALT study (NCT01537926) to determine the side  
18 effect and compliance profile of an oral formulation of NAC, and its effect on LV mass and other  
19 structural and functional indices 18.

## 21 **Conclusion**

22 Guideline driven medical practice has many benefits, not the least of which is the ability to extend  
23 standards for care of uncommon or challenging diseases to general cardiologists. Expert consensus  
24 reached during development of guidelines, however, cannot expect to capture the limitations in  
25 present understanding of complex clinical entities. Conflicting advice on the evaluation and  
26 management of HCM, for example, is largely a reflection of differences in the parsing of

1 incomplete albeit hard-won data on the disease. Herein we have sought to lay bare some of the  
2 strengths and shortcomings of the current knowledge base. The goal is transparency over dictum:  
3 transparency that although we have far deeper knowledge than we did 50 years ago, the lion's share  
4 of existing studies are observational, frequently single centre, and limited by historical context, and  
5 their findings generally concordant but far from monolithic. We encourage the practitioner to bring  
6 the power of expert consensus available in authored guidelines to the clinical setting, while  
7 maintaining a discerning posture towards the robustness of each recommendation. The role of  
8 subspecialist opinions and referral units also remains firmly intact, for there is no substitute for  
9 cumulative clinical and technical experience, dedicated facilities, and multidisciplinary support  
10 staff in the provision of nuanced care for patients in this perpetually evolving field. In reviewing  
11 both the unresolved issues and the frontiers of therapy, including the disease-preventing and -  
12 rescuing interventions that are finally on the horizon, we also anticipate the developments of the  
13 next half-century, both the far and the near.

14

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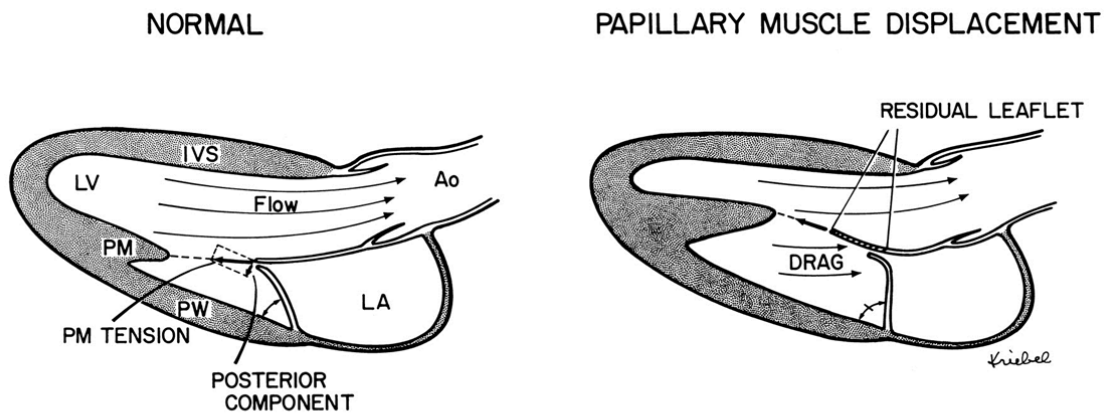
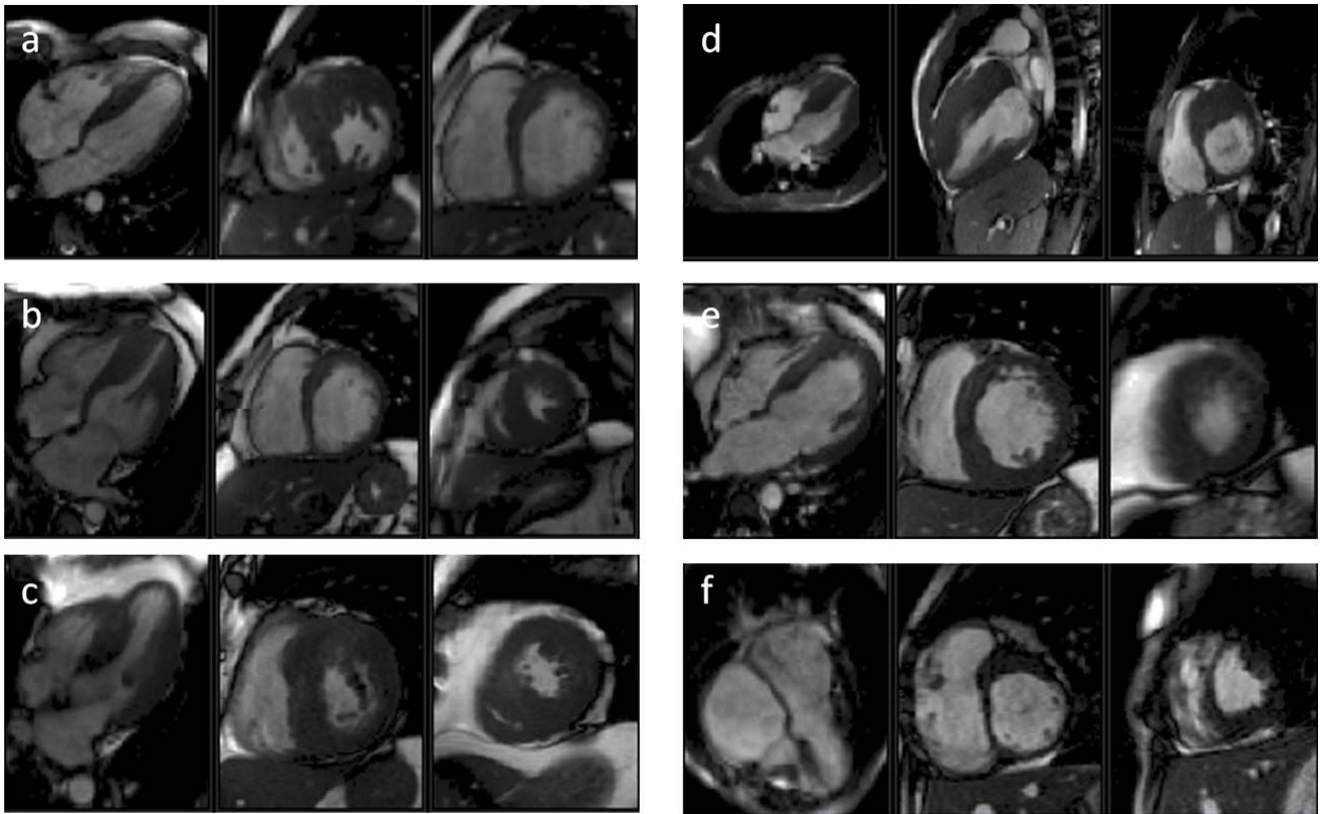


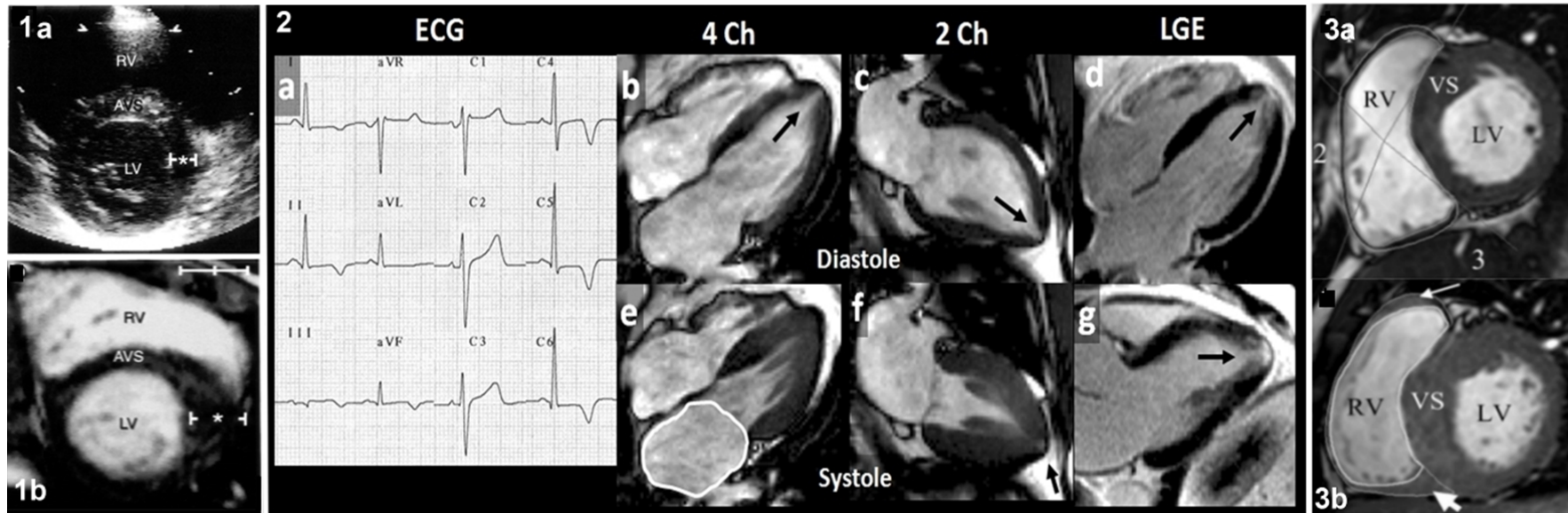
Figure 1. Systolic anterior motion of the mitral valve leading to left ventricular outflow tract obstruction and mitral regurgitation (After ref. 21, but please redraw)

Besides septal hypertrophy, a number of anatomical abnormalities contribute to systolic anterior motion of the mitral valve (SAM) and LVOTO in HCM. Anterior displacement of the papillary muscles places the mitral valve leaflets closer to the LVOT and pulls the posterior leaflet upwards so that it meets the anterior leaflet at its middle. The distal anterior leaflet is thereby left unrestrained, while incomplete coaptation results in mitral regurgitation. Also common in HCM are elongated valve leaflets and lax chordal structures, which render the residual portion of the leaflets longer and slacker, and still more prone to being dragged anteriorly by the flow of blood during systole.



**Figure 2. Cine cardiovascular magnetic resonance (CMR) images of HCM cases with *TNNI3* mutations [ref 48 - permissions needed]**

The spectrum of *TNNI3* disease offers a window on the diverse structural and functional abnormalities recognised in HCM, including: **(a)** asymmetrical anteroseptal hypertrophy (Arg162Gln); **(b)** apical hypertrophy (Arg162Gln); **(c)** midcavity obstruction (Arg145Trp); **(d)** severe biventricular hypertrophy (homozygous Arg141Gln mutation); and **(e)** burnt out phase (Arg186Gln). In some families, individuals with the same mutation in *TNNI3* may develop either HCM or a restrictive picture. Panel **(f)** shows restrictive cardiomyopathy in a child of six years from a *de novo* mutation in *TNNI3* (Lys178Glu).



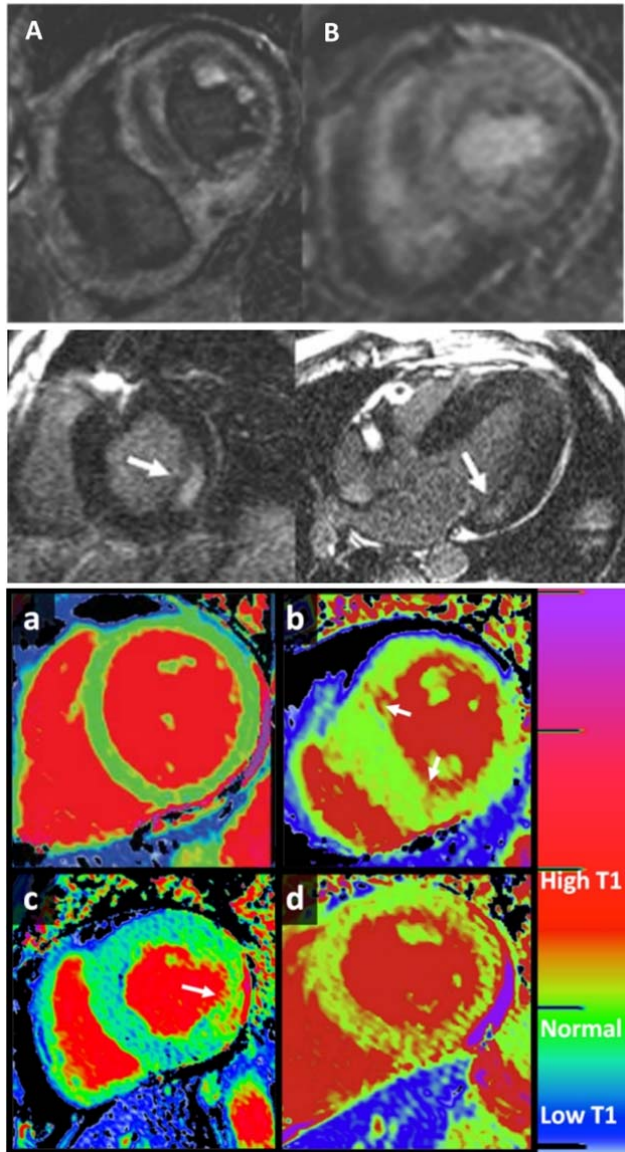
**Figure 3. Complementary role of echocardiography and CMR in the evaluation of HCM** (Panel 1,ref 53; panel 2, ref 54; panel 3, ref 57 - permissions needed)

Panel 1. Images are from a 13-year-old boy with nonobstructive HCM; 12-lead ECG showed poor R wave progression, inferior Q waves, and a deep S-wave in V2, but the echocardiogram (a) showed normal thickness in all LV wall segments, including the ventricular septum and contiguous portion of anterolateral free wall (\*). CMR (b) demonstrated 20mm of hypertrophy confined to the anterolateral LV free wall and a small part of the contiguous anterior septum (\*);

Panel 2 shows relative apical hypertrophy missed by echocardiography. An athletic 49-year-old man with no family history of HCM presented with atypical chest pain. 12-lead ECG showed deep inferolateral T-wave inversion, but coronary arteries were normal, as was the echocardiogram. CMR demonstrated: a discrete increase in wall thickness at the apex (10mm vs 8mm basally); a 14mm tube-like apical cavity (arrowed, b,c) which

obliterates in systole; a small apical micro-aneurysm un-obliterated in systole (arrowed, f); apical scar (arrows d, g); and left atrial dilatation (e). A mutation (R810H) was subsequently identified in MYBPC3.

Panel 3 shows (a) HCM with normal RVWT in the superior (1), anterior (2), and inferior (3) segments; and (b) HCM with increased RVWT in the superior segment (thin arrow) and extreme hypertrophy of the inferior segment (thick arrow).



**Figure 4. Late gadolinium enhancement (LGE) and T1 mapping in differentiation of archetypal HCM from phenotypic mimics (upper panel, ref 59; middle panel, ref 66 - permissions needed)**

Upper panel: Cardiac amyloidosis is characterised by dark blood pool and global subendocardial LGE (A), which becomes transmural (B) with progressive amyloid burden.

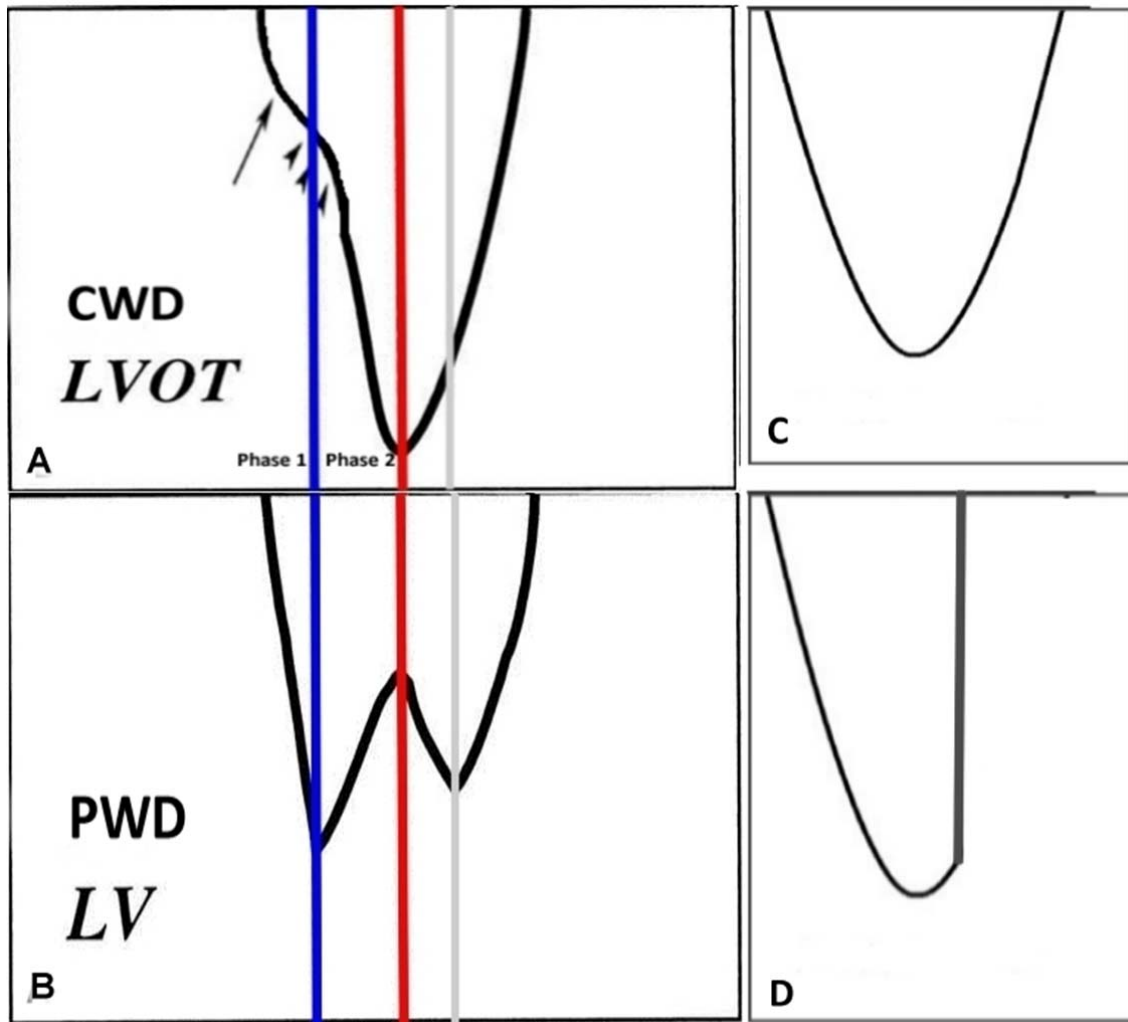
Middle panel: Short and long axis views of typical CMR findings in Fabry disease, including increased papillary muscle contribution to total LV mass, and LGE with a predilection for the basal inferolateral wall (arrows), both of which may arise in the absence of LVH. CMR may therefore identify latent cardiac involvement and prompt initiation of enzyme replacement therapy.

Lower panel: Native (noncontrast) myocardial T1 in short axis images in: (a) a healthy volunteer; (b) HCM, in this case with broadly normal myocardium apart from high T1 at the RV insertion points suggesting focal fibrosis; (c) Fabry disease, in which global attenuation of T1 (blue) likely reflects sphingolipid storage in the myocardium and may be observed prior to the onset of LVH. The high T1 signal at the basal lateral wall (arrow) indicates focal fibrosis; and (d) AL amyloidosis, with extensive T1 elevation (red).



**Figure 5. Aids and pitfalls in the Doppler echocardiographic assessment of LVOTO**

(Adapted from ref 93, 94, 96. Needs touching up/ redrawing. Please note that the right hand side of curve D, after the trough, should not be a vertical line - but rather a very steep downward curve.)



The dynamic nature of LVOTO in HCM gives rise to a CWD waveform often described as "dagger shaped" (A). In the presence of a gradient >60 mm Hg, the PWD trace at the entrance to the LVOT, apical to the mitral valve, may show the "lobster claw" abnormality (B).

Phase 1: Because there is no obstruction to LV outflow in early systole, the CWD trace is convex-to-the-left. As systole progresses, anterior motion of the mitral valve brings it into contact with the septum, with consequent onset of outflow obstruction.

Blue line: The inflection point on the CWD waveform corresponds to mitral-septal contact. If the obstruction is sufficiently severe, the ejection velocity within the LV cavity may fall by more than 50%, generating the first dip of the PWD trace (the "midsystolic drop").

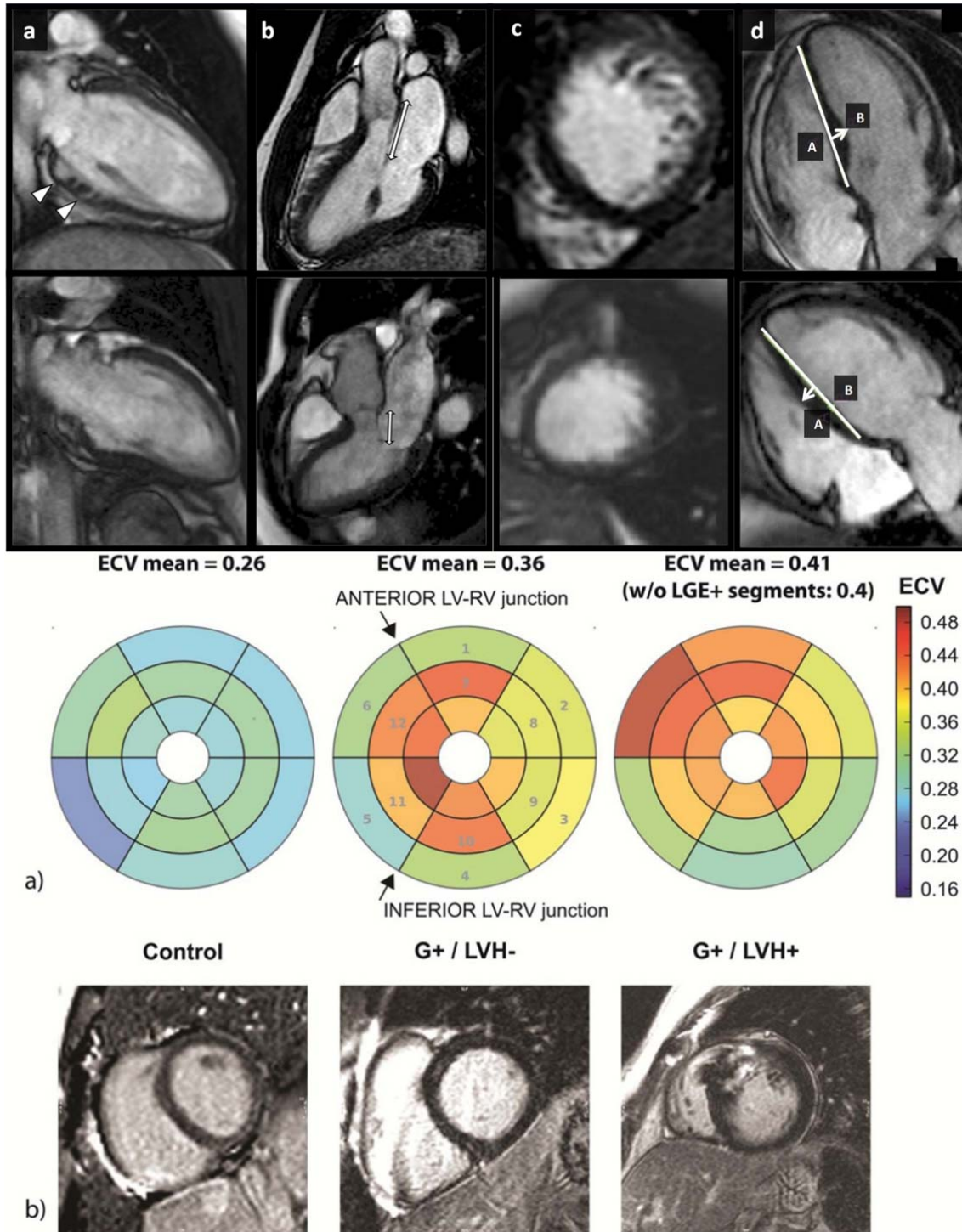
Phase 2: Thereafter, the rising pressure gradient causes narrowing of the LVOT diameter, which in turn increases the pressure gradient still further. This "amplifying feedback pattern" gives the CWD trace a concave-to-the-left shape after the inflection point.

Red line: The peak velocity in the LVOT coincides with the nadir of the velocity drop in the LV cavity, at which point the instantaneous pressure gradient is at its maximum. The LV cannot maintain ejection against the sudden rise in afterload, resulting in transient cessation of LV longitudinal shortening and closure of the aortic valve leaflets (tissue Doppler and M-mode not shown).

Grey line: The residual LV contents are ejected in late systole.

In contrast, the waveform of mitral regurgitation is usually symmetrical and bell-shaped (C). An estimated LV outflow velocity exceeding 5-5.5 m/s arouses suspicion of overlap with the mitral regurgitant trace and should prompt cautious re-interrogation of the Doppler signal.

A distinct entity is complete systolic emptying of a hyperdynamic LV. Here the CWD profile is asymmetric (D); once the peak velocity has been reached, the LV cavity is empty, so the trace returns to zero in late systole.



**Figure 6. CMR features of early (pre-LVH) HCM** (lower panel from ref 126 - permissions needed)

Upper panel. Top row: Genotype-positive LVH-negative subjects; bottom row: healthy controls. CMR has identified a number of structural abnormalities in genotype-positive LVH-negative subjects, including: a) clefts, often multiple; b) elongation of the anterior mitral valve leaflet; c) increased apical trabeculae and d) abnormal septal curvature. In the normal heart, the position of the interventricular septum is either neutral or convex into the right ventricle (d, lower), while in HCM it is convex into the LV (d, upper). Septal curvature is measured as the maximal distance from the LV endocardial border (B) to an intersection point (A) with a theoretical perpendicular joining the mid-septal wall at tricuspid valve insertion level with the apical right ventricular insertion point. The A-B distance is reportedly increased in mutation carriers ( $5.0 \pm 2.5$  mm vs.  $1.6 \pm 2.4$  mm,  $p \leq 0.0001$ ) vs. matched controls.

Lower panel. Segmental T1 measurements and mean ECV (top row) and LGE study (bottom row) in a typical healthy control, G+ LVH - gene carrier, and G+ LVH- HCM case. LGE is present in the G+LVH+ HCM case - prominently near the LV-RV junction - but does not allow discrimination between the G+LVH- gene carrier and the healthy control, being absent in both. In contrast, the G+LVH- gene carrier has elevated segmental T1 measurements and ECV relative to the control subject. The G+LVH+ HCM case demonstrates further expansion of the ECV, which remains highly abnormal even after exclusion of the LGE segments.

SECONDARY PREVENTION

PRIOR CARDIAC ARREST  
SPONTANEOUS SUSTAINED VT

All

Class I (strong) indication for ICD

PRIMARY PREVENTION

Family history of SCD

Maximal LV wall thickness<sup>a</sup>

Unexplained syncope

Non-sustained VT<sup>b</sup>

Abnormal BP response to exercise<sup>c</sup>

2003 consensus GUIDELINES\*†

principal risk factors

ANCILLARY risk factors

2011 ACCF/AHA Class IIA (Reasonable) indications for ICD

Any one of these Risk Factors

one of these risk factors

PLUS

Another risk factor or modifier

2014 ESC GUIDELINES: (HCM-Risk-SCD)

estimates probability of SCD at 5 years from  
these risk factors

Age at evaluation (-)<sup>d</sup>

LA diameter

LVOT obstruction (rest/ Valsalva)<sup>e</sup>

Extensive LGE on CMR

>1 mutation (Double/ compound/ triple)

IV apical aneurysm

Coexisting obstructive coronary artery disease

Microvascular ischaemia

Paced ventricular electrogram fractionation<sup>f</sup>

(Prior alcohol septal ablation)

(burnt OUT DISEASE)

## Figure 7. Risk Stratification in HCM.

Footnotes:

\* Inherent limitations of the 2003 algorithm include the assignment of equal weighting to all 5 principal risk factors without regard for different effect sizes, and assumption of cumulative risk via a simple additive model, without allowing for the possibilities of multiplicative interaction, specific interactions between markers, or modification by ancillary markers.

† Some of the ancillary predictors (e.g., paced electrogram fractionation) were published subsequent to the 2003 consensus guidelines.

a. Maximal LV wall thickness (MWT) is entered as a continuous variable into HCM-Risk-SCD. In contrast, both the 2003 consensus and 2011 American guidelines dichotomise MWT, with the cut-off for high risk arbitrary set at  $\geq 30$ mm

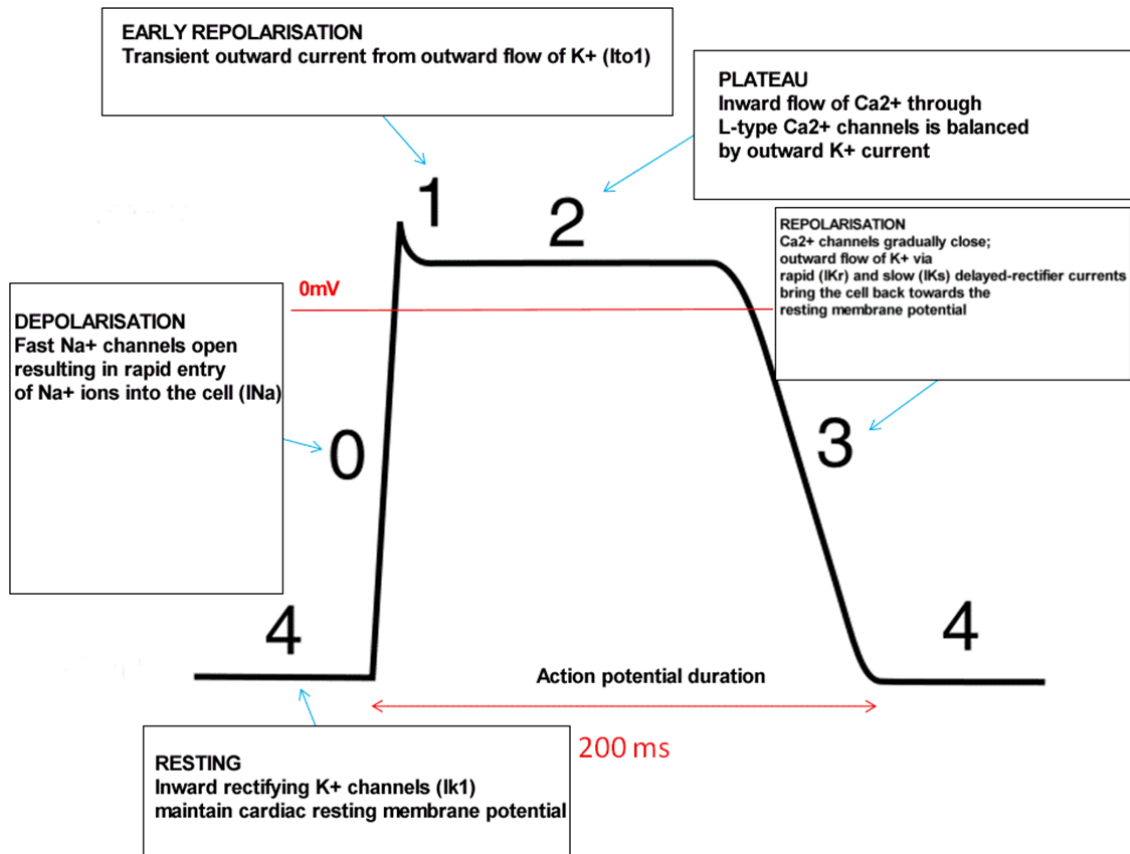
b.  $\geq 3$  consecutive beats at  $\geq 120$  bpm

c. Failure of systolic BP to rise by  $\geq 20$  mm Hg during maximal upright exercise testing - prognostic impact greatest under the age of 40

d. Age had a negative regression coefficient in HCM-risk-SCD

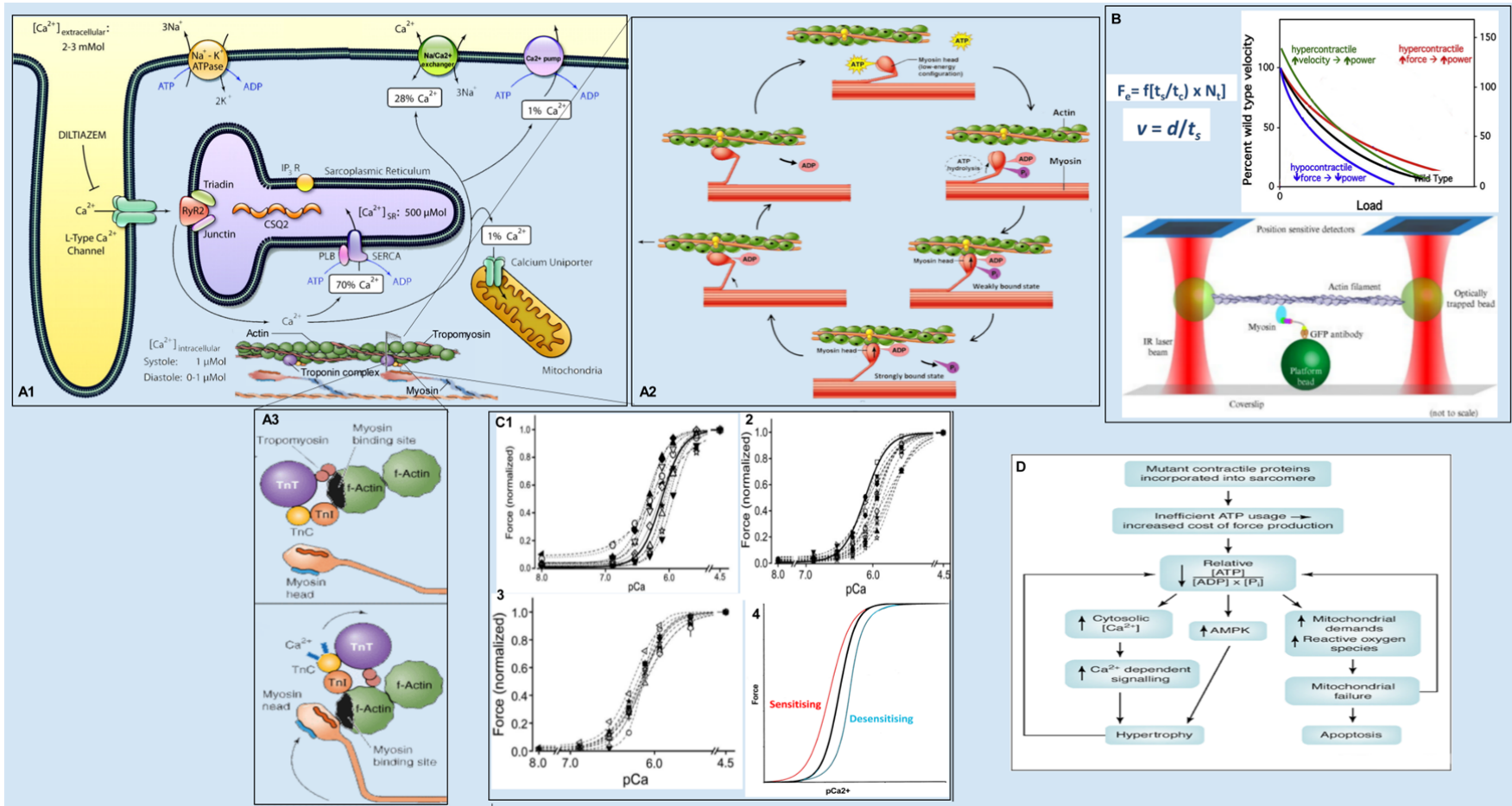
e. LVOT gradient is entered as a continuous variable into HCM-Risk-SCD, while other studies/ algorithms generally use  $\geq 30$  mm Hg as the cut-off

f. Paced electrogram fractionation analysis was evaluated in 179 HCM cases followed up for a mean of 4.3 years and reported to have a C-statistic of 0.88 for prediction of SCD/ resuscitated VF arrest.



**Figure 8.** Action potential of a normal cardiac myocyte (after ref 196; please redraw - would be better as inset to figure 8, but not sure how to achieve this - it's already a mammoth figure)





**Figure 9. Targets for substrate-modulating therapy in HCM.** (A1-3 - needs redrawing, preferably from scratch; we do not need to show Triadin/ Junctin in A1)

*Panel A.* Calcium handling in the cardiac myocyte is shown in A1; the sarcomere and troponin-tropomyosin complex are magnified in A2 and A3, respectively. The myosin head binds strongly to ATP. ATP is hydrolysed to ADP and inorganic phosphate (Pi), which remain bound to myosin; the energy released locks the myosin head into a pre-stroke configuration (A2). Voltage-gated L-type  $\text{Ca}^{2+}$  channels open during phases 0 and 1 of the cardiac myocyte action potential, allowing a small influx of  $\text{Ca}^{2+}$  ions. This in turn activates cardiac ryanodine receptors (RyR2), which trigger much greater release of stored, calsequestrin-bound  $\text{Ca}^{2+}$  ions from the sarcoplasmic reticulum (calcium-induced calcium release [CICR]) (A1). The rapidly rising cytosolic calcium activates troponin C, inducing a conformational change in the troponin-T-I-C complex, which pulls tropomyosin out of its groove on the actin filament. Lying exposed on the actin filament now are binding sites for myosin (A3).

Myosin-ADP-Pi binds to actin, weakly at first. Pi is subsequently released, resulting in stronger binding of myosin-ADP to actin. This weak to strong transition is generally the rate-limiting step in the actin-myosin crossbridge cycle. The myosin power stroke happens next (force producing state). Subsequent release of ADP frees the myosin head to dissociate from actin and bind preferentially to ATP again (A2). The cycle repeats, with myosin binding actin monomers progressively closer to the Z disk, as long as the cytosolic calcium concentration remains high.

Relaxation of the cardiac myocyte during diastole is dependent on calcium being (1) extruded from the cell by the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger and the sarcolemmal  $\text{Ca}^{2+}$  pump; and (2) sequestered back into the sarcoplasmic reticulum by the SERCA2a pump, which is inhibited by dephosphorylated phospholamban (PLN) (A1).

*Panel B.* The upper equation enables calculation of the ensemble force ( $F_e$ ) of the sarcomere as the product of the intrinsic force of each myosin head ( $f$ ), the total number of myosin heads functionally able to interact with with actin filaments ( $N$ ), and the ratio of the time spent in a strongly-bound state to the total cycle duration ( $t_s/t_c$ ) - which determines the proportion of myosin heads in a force-producing state. The lower equation estimates the unloaded velocity ( $v$ ) from the myosin head stroke size ( $d$ ) divided by the strongly-bound state time ( $t_s$ ).

The power output of the sarcomere is represented by the area under the load-velocity curve (graph). As the ensemble force and/or velocity increase, so does the power output.

Also shown is a dual-beam, three-bead optical trap. Both ends of a single actin filament are attached to 1  $\mu\text{m}$  polystyrene beads, which are held in place by two focused infrared laser beams. Beneath this "actin dumbbell" is a single myosin molecule attached to a 1.5  $\mu\text{m}$  polystyrene platform bead fixed on a coverslip surface. The position-sensitive detectors can accurately gauge even 1nm of movement in the beads. This assay allows direct measurement of the intrinsic force ( $f$ ), strongly bound state time ( $t_s$ ), and stroke size ( $d$ ) of a myosin head.

*Panel C.* Force-pCa curves illustrating the relationship between calcium concentration (pCa) and active force generation in soleus muscle biopsies from two HCM cases with Ca<sup>2+</sup> sensitising (1) and desensitising (2) mutations in *MYH7* (with the wild-type force-pCa relation appearing as a heavy solid line) and a control subject (3). Averaging of the curves (4) from the individual muscle fibres reveals the overall effect of the sensitising and desensitising mutations as a shift to the left and right respectively, but masks an equally conspicuous finding: increased divergence between the constituent fibres in the mutated muscle samples vs the control.

*Panel D.* The energy depletion hypothesis.

### **Box 1. Aids and Pitfalls in the Pathological Diagnosis of HCM**

- The site and extent of LVH in HCM vary considerably. RV hypertrophy also is heterogeneous and may be concentric or localised to the apex, mid-septum, basal septum, and/or free wall. Prominent basal septal hypertrophy ("sigmoid septum") is not diagnostic of HCM unless accompanied by myocyte disarray.
- Both interstitial and replacement fibrosis occur in HCM. Septal endocardial fibrosis just below the aortic valve ("subaortic mitral impact lesion") is suggestive of HCM but not pathognomonic, also occurring (albeit rarely) in systemic hypertension, aortic stenosis, and isolated basal septal hypertrophy. Diffuse endocardial thickening is non-specific and observed in conjunction with a wide range of pathologies.
- Arteriolar density may be reduced in HCM. Small intramural vessels may show intimal and medial smooth muscle cell hyperplasia, with narrowing of the lumen, and are often surrounded by dense perivascular collagen.
- Myocyte disarray refers to haphazard alignment of adjacent myocytes (e.g., perpendicular/oblique rather than parallel); distribution is typically regional and may not coincide with the localisation of hypertrophy. Detection is aided by extensive sampling of the full circumference at basal, mid-ventricular, and apical levels, using transverse rather than longitudinal sections. Although requisite for diagnosis of HCM, myocyte disarray is non-specific, arising to a more limited extent in other settings including congenital cardiac anomalies. In the normal heart, small areas of disarray may be present in trabeculations and where the right ventricle interdigitates with the septum; the latter is often associated with interstitial adiposis. There is no consensus regarding the minimum extent of myocyte disarray necessary for confirmation of HCM, although 10% has been recommended.
- Cardiac myocytes in HCM may have enlarged, pleomorphic, and/or hyperchromatic nuclei and/or disorganised myofibrillary architecture.

- Sarcoplasmic vacuolisation in H&E stained sections arouses suspicion of metabolic storage disease.

## Box 2. Emerging Applications for CMR in HCM

Gadolinium-based contrast agents (Gd-contrast) diffuse into the interstitial space without crossing intact cell membranes. A localised delay in the washout of Gd-contrast suggests coincident expansion of the space available for it, due - for example - to myocyte loss, fibrosis, or an infiltrative process. The paramagnetic properties of Gd-contrast result in shortening of T1 relaxation times in the region affected, generating a bright signal against the nulled normal myocardium in T1-weighted images. CMR with late gadolinium enhancement (LGE) thereby facilitates diagnosis of phenotypic mimics of HCM.

Studies of the prognostic role of LGE in HCM have reported associations with progressive LV remodelling (wall thinning, increasing end-systolic dimension), development of LV systolic dysfunction, deterioration to NYHA functional class III-IV, hospitalisation for heart failure, heart failure-related death, ventricular tachycardia, cardiovascular mortality, and all-cause mortality. Evidence of influence on arrhythmic outcome is less strong; at present, LGE has not been definitively established as an independent predictor of SCD. Possible reasons for the mixed results include differences in case mix and follow-up duration, in the rigour with which conventional risk profiling was performed, in the power achieved, and in the approach used to quantify LGE.

LGE dichotomises myocardium into bright (enhanced) vs dark (nulled), an oversimplification with twofold implications. First, quantification of LGE is based on an operator-defined threshold of signal intensity, which might be anything from 2-6 standard deviations above normal myocardium, or assume full width at half maximal signal (FWHM), or entail manual delineation of "regions of interest". Techniques that offer a passable approximation of the volume of a well-demarcated scar will prove more limited

when applied to disease states such as HCM, wherein fibrosis is less cohesive. Accordingly, the reproducibility of all quantification methods appears poorer in HCM than acute or chronic myocardial infarction, although FWHCM may be the most reliable. Second, the absence of a reference region of normal myocardium renders LGE unsuitable for imaging diffuse fibrosis, which may generate an almost uniform myocardial signal intensity.

An emerging solution to the challenge of visualising diffuse processes is T1 mapping - direct measurement of the longitudinal relaxation time (T1) in different areas of the myocardium.

Cardiac T1 mapping before and after administration of Gd-contrast allows estimation of the myocardial volume of distribution of Gd, which reflects the extracellular volume fraction (ECV). The ECV is expanded in the presence of interstitial fibrosis. Available data indicate good correlation between ECV estimates from T1 mapping and the collagen volume fraction on histology. Combined evaluation of focal and diffuse fibrosis using both LGE and T1 mapping techniques may enhance the utility of CMR as a prognostic tool in HCM.



### **Box 3. Special Considerations in Children with Hypertrophic Cardiomyopathy**

- The genetic profile of isolated HCM in children, whether sporadic or familial, includes a ~50% prevalence of sarcomeric mutations, most commonly in MYH7 and MYBPC3 - similar to that in adults.
- Vigilance for pheno- and genocopies of HCM takes on even greater importance in children. Infants born to diabetic mothers, for example, may have symptomatic LVH, RV hypertrophy, and/or LVOTO, but abnormalities typically resolve within the first 6 months of life. Timely diagnosis of inborn errors of metabolism allows commencement of substrate-modulating therapies, ranging from nutritional restriction in type 1 tyrosinaemia to enzyme replacement, which may reverse or forestall progression of the cardiac phenotype.
- Morbidity, mortality, and cardiac transplantation rates appear highest among children with inborn errors of metabolism, mixed functional phenotypes (HCM with dilated/restrictive cardiomyopathy), malformation syndromes, or presentation in infancy.
- More favourable outcomes have been reported in children with isolated HCM diagnosed at age $\geq$ 1. Among children with isolated HCM receiving ICDs for primary prevention, however, the annual incidence of appropriate intervention may be as high as 3.1%. Offsetting this is device-related complication rate of 9.5%/year, and greater prominence of psychosocial adjustment issues, which emphasise the need for reliable risk stratification in paediatric HCM.
- Development of a dedicated prognostic algorithm from existing data is impeded by heterogeneous inclusion criteria and frequent use of a combined endpoint, with few studies discriminating between arrhythmic and non-arrhythmic (heart failure related) events. Proposed indicators of adverse outcome in isolated HCM include congestive heart failure, low weight, severe LVH, abnormal blood pressure response to exercise,

LA size, reduced LV fractional shortening, decreased early transmitral flow velocity, non-sustained VT, and QTc dispersion, with the latter two purportedly specific for arrhythmic outcome.

#### **Box 4. Aids and Pitfalls in the Doppler echocardiographic assessment of LVOTO**

Continuous-wave Doppler (CWD) allows measurement of the peak LVOT velocity ( $v$ ), from which the maximal instantaneous gradient is calculated ( $\Delta P=4v^2$ ). The anatomical level of the obstruction is pinpointed by sequential interrogation from LV apex to outflow with pulse-wave Doppler (PWD). Reliable assessment requires obtaining an acoustic window with a well-opened LVOT and high quality spectral images, which can be tricky in the setting of distorted LV geometry, such as a bulging thickened anterobasal septum. The challenge is compounded during exercise testing by upright posture and rapid, strenuous respiratory movements.

The main pitfall, however, is contamination of the LV outflow waveform by coexisting mitral regurgitation. The systolic anterior motion of the mitral valve that underlies LVOTO is almost always accompanied by an inferolaterally directed jet of mitral regurgitation, which arises in mid-to-late systole in **close anatomical proximity to the** outflow stream. (A mitral regurgitant jet that is centrally or anteriorly directed, on the other hand, warrants further investigation for intrinsic mitral valve abnormalities). Notwithstanding a sometimes trivial appearance on colour flow, the mitral regurgitation signal on CWD is usually strong.

Discrimination between the two jets is dependent on recognising their characteristic profiles **(Figure 5A-C)**.

Two other disease states occasionally confused with obstructive HCM are aortic stenosis and subaortic stenosis (either discrete or diffuse). Both are fixed obstructions present throughout systole, conferring on the CWD waveform a smoother contour and earlier peak. The third entity that warrants exclusion is the spurious obstruction caused by complete systolic emptying of a hyperdynamic LV (**Figure 5D**). Absent in all three states are systolic anterior

motion of the mitral valve, mitral-septal contact, an inflection point on the CWD trace, and the lobster claw abnormality on PWD (Figure 5).

### Box 5. Phenotypic features of early (pre-LVH) HCM

- Tissue Doppler echocardiography has detected abnormalities in mitral annular velocities in pre-LVH familial HCM, but is limited by angle-dependency. Increased peak late diastolic annular velocities have also been demonstrated by speckle-tracking echocardiography, but discrepancies in existing data hinder clinical application at present.
- CMR studies in carriers of HCM-related mutations have revealed a number of structural and functional abnormalities that precede the development of LVH, including:
  - (i) Lower end-systolic volumes ( $38\pm 9$  vs  $43\pm 12$  ml in controls);
  - (ii) Clefts are narrow recesses in the LV wall, blood-filled and contiguous with the LV cavity, with a depth of  $\geq 50\%$  the thickness of the adjacent myocardium. Observed during diastole, clefts show at least partial systolic obliteration. The presence of  $\geq 1$  cleft is twice as common among carriers of mutations in MYBPC3 than other genes (47% vs 23%,  $p=0.045$ ). Diagnostic utility depends on both location and number, with multiple clefts showing higher specificity but lower sensitivity for mutation carriership. Clefts appear less prevalent in overt HCM, regressing perhaps as the LV wall remodels, or becoming less easy to identify owing to diastolic compression by the thickened myocardium.
  - (iii) The anterior leaflet of the mitral valve appears longer in mutation-carriers than matched control subjects ( $21\pm 3$  versus  $18\pm 3$  mm).
  - (iv) Apical LV trabeculation is more prominent among mutation-carriers than controls ( $1.25\pm 0.07$  vs  $1.20\pm 0.05$ ), as quantified in terms of fractal dimension, a unitless measure of the geometric complexity of a structure.
- A combination of parameters (i)-(iv) discriminates mutation carriers from healthy controls with an area under the ROC curve of 0.85. More recently described on CMR examination of LVH-negative mutation carriers is abnormal septal convexity.
- There are rare reported cases of mutation carriers in whom symptomatic latent LVOTO - confirmed by exercise stress echocardiography - was the first clinical manifestation of the disease, preceding the development of LVH by  $\sim 2$  years. Pre-LVH abnormalities in mitral valve leaflet dimensions have been invoked as a possible predisposing factor. (It should be noted, however, that exercise and dobutamine

stress echocardiography may unmask latent LVOTO in many healthy subjects without LVH, and that its presence - outside the context of familial HCM - is non-specific).

- Serum levels of the C-terminal propeptide of type I procollagen (PICP) also are elevated in LVH-negative mutation carriers ( $107.73 \pm 4.65$   $\mu\text{g}$  per liter vs  $82.16 \pm 3.03$   $\mu\text{g}$  per liter in controls,  $p < 0.001$ ), suggesting early activation of profibrotic pathways. The LGE technique allows visualisation of focal fibrosis, but existing CMR studies indicate that this does not appear until later in the disease course, following the onset of LVH. Emerging data suggest, however, that expansion of the extracellular matrix begins earlier and progresses in line with the disease. CMR estimates of ECV were  $0.27 \pm 0.01$  in controls vs.  $0.33 \pm 0.01$  in LVH-negative mutation carriers vs.  $0.36 \pm 0.01$  in LVH-positive HCM cases.

### **Box 6. Invasive septal reduction therapies explained**

Septal myectomy entails thoracotomy, cardiopulmonary bypass, and resection of the hypertrophied basal septum via transaortic approach or - less commonly - through the left atrium and mitral valve. Besides the complications pertaining to general anaesthesia and open heart surgery in general, there is a risk (<2%) of aortic dissection and/or aortic or mitral valve injury. Surgical candidates can expect a ~5-day initial hospital stay and significant postoperative recovery time. Gradient alleviation, however, is immediate. Resection can be customised to the sometimes complex anatomy of the outflow tract and extended distally in the presence of midcavity obstruction (more data on risks/ benefits awaited). Often performed in conjunction with mitral valve interventions such as repair, plication, replacement, or papillary muscle realignment, myectomy can also be combined with other surgical procedures, such as coronary artery bypass grafting or aortic valve replacement.

Alcohol septal ablation is a percutaneous procedure offering shorter hospital stay and more rapid recovery. The general complication profile is similar to angioplasty, with the added risk (7-20%) of permanent pacemaker implantation, which is ~twofold higher than that associated with myectomy. Feasibility depends on the availability of a septal perforator that supplies a territory confined to the obstructive part of the hypertrophic septum. Contrast echocardiography facilitates delineation of the area of perfusion; if it does not include the target septal segments, or extends to remote regions of the myocardium, another septal perforator is cannulated or the procedure abandoned. Selection of a suitable branch of the LAD is followed by alcohol injection to induce localised myocardial necrosis. Many subjects demonstrate a triphasic haemodynamic response, with immediate marked relief of LVOTO secondary to stunning or myocardial oedema. As the myocardium recovers from the initial

insult, however, the gradient may return to 50% of its preprocedure level; sustained reduction ensues gradually over weeks to months as scarring, thinning, and remodelling occur.

Dual chamber (DDD) pacing is purported to alleviate LVOTO by two main mechanisms.

During systole, RV apex pacing results in paradoxical movement of the IVS, which increases the dimensions of the LVOT. During diastole, the AV interval is programmed such that the timing of atrial systole allows maximal LV filling. Small ( $n < 100$ ) observational studies and randomised trials suggest that DDD pacing effects modest gradient reduction, with subjective symptomatic benefit; objective improvement in functional capacity has been reported in the  $>65$  age group. As such, it is offered second-line when other interventions are too high risk or have been declined. For HCM cases requiring dual-chamber pacemakers for other indications, however, it makes sense - in the first instance - to optimise settings for relief of LVOTO. A more recent innovation under further investigation is the use of biventricular pacing to reduce LVOTO in HCM cases with indications for ICD therapy and/or contraindications to septal myectomy and alcohol septal ablation. Pilot series involving 11-12 subjects reported improvements in NYHA class and objective measures of exercise capacity, with progressive reduction in both the LVOT gradient and the grade of mitral regurgitation over 1-3 years, accompanied - in one study - by regression of LVH. The benefits have been tentatively ascribed to altered contraction of a large area of the LV, with earlier longitudinal displacement of the lateral wall and diminished peak longitudinal displacement of the septum.



Table 1. Clinical complications of HCM with recommended medical therapy

FUNCTIONAL CONSEQUENCE	CLINICAL MANIFESTATIONS	OPTIONS FOR PHARMACOTHERAPY
Diastolic dysfunction	Dyspnoea Reduced exercise capacity	<ul style="list-style-type: none"> <li>Beta-blockers, regardless of whether there is coexisting LVOTO</li> <li>Non-dihydropyridine calcium channel blockers (verapamil or diltiazem), used with caution in the presence of significant LVOT gradient</li> </ul>
Left ventricular outflow tract obstruction (LVOTO), mitral regurgitation	Chest pain Dyspnoea Reduced exercise capacity Symptoms of impaired consciousness	<ul style="list-style-type: none"> <li>Resting LVOT gradient <math>\geq 30</math> mm Hg is reportedly a predictor of both all-cause mortality and arrhythmic events, but whether pharmacotherapy reduces this risk is currently unresolved. The incidence of SCD in asymptomatic individuals with resting LVOTO as their sole risk factor is estimated at <math>&lt;0.4\%</math>, strengthening the argument against intervention for purely prognostic reasons. Pending further data, treatment is directed at symptom relief.</li> <li>General advice is to ensure adequate filling and avoid vasodilators such as amlodipine and positive inotropic agents such as digoxin</li> <li>Non-vasodilating beta-blockers are used first line and are particularly effective for exertional LVOTO</li> <li>Disopyramide as add-on to beta-blockers, particularly for symptomatic resting LVOTO; dose is titrated according to tolerance of anticholinergic side effects. Monitoring of QT interval advised, with avoidance of other QT-prolonging agents (e.g., amiodarone, sotalol)</li> <li>Disopyramide plus verapamil/ diltiazem if beta-blockers are contraindicated</li> <li>Disopyramide should not be used as monotherapy in the presence of Afib because it may accelerate the ventricular response rate.</li> <li>Verapamil/ diltiazem may also be used as monotherapy if beta-blockers are contraindicated, but caution is warranted, particularly in the presence of severe LVOTO</li> <li>In the rare setting of hypotension and/ or pulmonary oedema secondary to acute LVOTO, patients who do not respond adequately to filling may benefit from IV beta-blockers and/ or vasoconstrictors such as phenylephrine</li> <li>Invasive septal reduction for NYHA class III/IV symptoms despite maximum tolerated pharmacotherapy</li> </ul>
Ischaemia	Chest pain, dyspnoea >2 mm ST-segment depression on exercise (usually far deeper) Reversible defect on perfusion scan	<ul style="list-style-type: none"> <li>If obstructive coronary artery disease is unlikely or has been excluded, microvascular ischaemia can be presumed. Non-dihydropyridine calcium channel blockers such as verapamil or diltiazem are often used first line in this setting; beta-blockers are an alternative.</li> </ul>
Afib	Palpitation Dyspnoea Presyncope/ Syncope	<ul style="list-style-type: none"> <li>Consider anticoagulation (CHA2DS2-VASc Score not recommended in HCM)</li> <li>Rhythm control with sotalol or amiodarone (with variable success)</li> <li>Rate control with beta-blockers or non-dihydropyridine calcium channel blockers</li> </ul>
Ventricular arrhythmia	Palpitation Presyncope/ syncope	<ul style="list-style-type: none"> <li>Non-sustained VT on ambulatory ECG monitoring is a risk factor for SCD. Amiodarone +/- beta-blockers may suppress ventricular extrasystoles and non-sustained VT and appeared, in studies from the pre-ICD era, to confer a survival benefit. In contemporary practice, however, ICD therapy is first line for individuals with a high risk profile.</li> <li>Sustained VT is uncommon and warrants evaluation for coexisting coronary artery disease and/ or LV apical aneurysm with adjacent scarring (which may be amenable to ablation). ICD is indicated for prevention of SCD; anti-arrhythmic therapy with beta-blockers and/ or amiodarone may be of benefit in suppressing symptoms</li> </ul>
Abnormal vascular responses	Symptoms of impaired consciousness  Failure of systolic BP to rise by $\geq 20$ mm Hg during maximal upright exercise testing or fall $>20$ mm Hg from peak pressure	<ul style="list-style-type: none"> <li>Although numbers remain small, the selective serotonin reuptake inhibitor paroxetine has been shown to reverse paradoxical vasodilation, alleviate associated symptoms, and augment systolic blood pressure in HCM cases with an abnormal blood pressure response to upright exercise.</li> <li>Pharmacological therapy for vascular instability has the potential to be of both symptomatic and risk-modifying benefit, but remains largely empirical until further data become available.</li> </ul>
Wall thinning and cavity dilation	Symptoms of heart failure	<ul style="list-style-type: none"> <li>Conventional therapy for systolic heart failure (including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, diuretics if necessary)</li> </ul>

Table 2. Phenotypic Mimics of Hypertrophic Cardiomyopathy

	Phenocopies	Genocopies
Heritability	Non-heritable	Heritable
Examples	<p>Isolated basal septal hypertrophy LVH in the setting of: Phaeochromocytoma Acromegaly AL and wild type TTR amyloidosis Exposure to drugs such as anabolic steroids, tacrolimus, and hydroxychloroquine.</p>	<p><u>Inborn errors of metabolism</u> Impaired handling of: Carbohydrates (e.g., glycogen storage disorders Pompe and Danon) Amino acids (e.g., Type 1 tyrosinaemia) Fatty acids (e.g., carnitine deficiency)</p> <p><u>Lysosomal storage diseases</u>- e.g., Anderson-Fabry disease (AFD)</p> <p><u>Mitochondrial cytopathies</u>- e.g., Friedreich's ataxia, Leber's hereditary optic neuropathy, Sengers syndrome</p> <p><u>RASopathies</u>- e.g., Noonan, LEOPARD, Costello, cardiofaciocutaneous syndrome</p> <p><u>Lipodystrophic syndromes</u></p> <p><u>Neuromuscular disorders</u> -e.g., Myofibrillar myopathy types 1 and 2</p>
Diagnosis	Symptoms, signs, ECG, and imaging abnormalities that are red flags for phenotypic mimics listed in 2014 ESC guidelines. Extracardiac features occasionally are lacking; e.g., expression of cardiac variant AFD is confined to the heart. Routine measurement of plasma alpha-galactosidase A levels has uncovered AFD at a prevalence ranging from 0.5% in unselected HCM cohorts to 6% and 12% among men and women with late-onset disease respectively.	
Impact on management	<ul style="list-style-type: none"> <li>Interventions that are highly effective in archetypal HCM cases may be less so in phenotypic mimics - e.g., failure of ICDs to restore normal rhythm in many patients with Danon disease (<i>LAMP2</i> cardiomyopathy)</li> <li>Treatments that target the underlying biochemical derangement are becoming available and may halt progression or reverse the cardiac manifestation. In amyloidosis, for example, treatment options include tetramer stabilisers (Tafamidis and Diflunisal) and doxycycline/tauroursodeoxycholic acid to slow progression; investigational therapies such as gene silencing by antisense oligonucleotides or small interfering RNA; conjunctive use of CPHCP and antibodies to human serum amyloid P to clear circulating amyloid from both plasma and visceral deposits.</li> </ul>	
	<p><u>Acromegaly</u> Successful control of growth hormone/ insulin-like growth factor excess results in reduced LV mass and improvement in diastolic function</p> <p><u>Tacrolimus-induced HCM</u> Resolution/ regression observed with dose reduction or discontinuation</p>	<p><u>Inborn errors of metabolism</u> Specific interventions include nutritional restriction/ supplementation, substrate reduction, enzyme replacement, molecular chaperone therapies, e.g.: Recombinant human <math>\alpha</math>-galactosidase A in AFD Alglucosidase alfa in Pompe Idebenone in Friedreich's ataxia</p>
Disease profile and natural history	Frequently distinct from that of sarcomeric HCM. Vigilance for extracardiac features may be necessary.	
	<p><u>Isolated basal septal hypertrophy</u> More common with increasing age</p> <p><u>LVH in infants of diabetic mothers</u> Typically resolves spontaneously within first 6 months of life</p>	<p><u>AFD</u> Increased risk of CVA Declining GFR (may be slowed by combined therapy with agalsidase alpha and renin-angiotensin system inhibitors)</p> <p><u>PRKAG2 (AMP kinase) disease</u> Progressive conduction system disease Ventricular preexcitation</p> <p><u>Danon disease</u> Early severe LVH, followed by cavity dilation and systolic dysfunction with rapid deterioration to endstage heart failure</p>
Impact on family screening	Not indicated	<p>Inheritance pattern is disease-specific and an important consideration during family screening and genetic counselling, e.g.:</p> <p><u>Autosomal dominant</u> <i>PRKAG2</i> mutations, RASopathies</p> <p><u>Autosomal recessive</u> Abnormalities of carbohydrate, amino acid, and fatty acid handling</p> <p><u>X-linked</u> Anderson-Fabry disease Danon disease (<i>LAMP2</i> cardiomyopathy)</p> <p><u>Mitochondrial</u> Friedreich's ataxia</p>

Table 3. Clinical Work-up in HCM

Clinical history	<p><u>Chest pain</u> ?Ischaemia ?LVOTO</p> <p><u>Dyspnoea/ reduced exercise tolerance</u> ?Diastolic dysfunction ?LVOTO ?Mitral regurgitation ?Systolic impairment</p> <p><u>Palpitation</u> ?Supraventricular arrhythmia ?Ventricular arrhythmia</p> <p><u>Symptoms of impaired consciousness</u> ?LVOTO ?Abnormal vascular responses ?Supraventricular arrhythmia ?Ventricular arrhythmia Unexplained syncope is a risk factor for SCD</p> <p><u>Extracardiac symptoms</u> ?Phenotypic mimic</p>
Physical examination	<p>Signs of LVOTO/ mitral regurgitation/ atrial fibrillation Extracardiac signs suggestive of phenotypic mimics</p>
Pedigree	<p>Minimum three generations with particular focus on SCD, CVA (especially age &lt;50), and heart failure Family history of SCD is a risk factor for arrhythmic events</p>
12-lead ECG	<ul style="list-style-type: none"> <li>• Pathological Q waves and/or T-wave flattening/ inversion in the lateral and/or inferior leads, which are of particular value in distinguishing load-induced LVH from HCM.</li> <li>• Other findings in HCM include P-wave changes suggestive of LA dilation, left axis deviation, LBBB</li> <li>• Shortened PR intervals and slurring of the upstroke of the QRS complex may be present in HCM cases without underlying accessory pathways</li> <li>• Isolated voltage criteria for LVH are common in young people and do not <i>per se</i> raise suspicion of HCM</li> <li>• Persistent atrial fibrillation is associated with increased risk of thromboembolism</li> </ul>
Echocardiography	<p><u>Transthoracic echocardiogram</u></p> <ul style="list-style-type: none"> <li>• Recommended during screening examinations/ at baseline, at follow-up as part of prognostic assessment, and following onset of new symptoms/ event</li> <li>• Comprehensive 2D-study including assessment of LV wall thickness at different levels, systolic and diastolic function, left atrium, mitral valve, LV outflow tract, and RV involvement. RVWT reportedly correlates with NYHA class and is independently related to the presence of non-sustained VT in HCM.</li> <li>• Indications for exercise stress echocardiography are discussed in the text</li> </ul> <p><u>Contrast echocardiogram</u></p> <ul style="list-style-type: none"> <li>• Administration of an intravenous contrast agent improves endocardial definition and may facilitate visualisation of LV apex.</li> <li>• In candidates for alcohol septal ablation, intracoronary injection of contrast is mandatory prior to alcohol administration to ensure exclusive localisation to the basal septum at the point of mitral-septal contact</li> </ul> <p><u>Transoesophageal echocardiogram</u></p> <ul style="list-style-type: none"> <li>• Assessment of mitral valve apparatus if intrinsic valve abnormalities suspected or invasive septal reduction planned.</li> <li>• Intraoperative guidance of surgical myectomy</li> </ul>
Exercise ECG	<ul style="list-style-type: none"> <li>• Indicated as part of prognostic assessment; may also shed light on symptoms</li> <li>• If the systolic BP falls or fails to rise by <math>\geq 20</math> mm Hg (flat response) during maximal upright exercise testing, vascular instability is likely present - a predictor of SCD</li> <li>• May unmask ischaemia, which is associated with increased risk of adverse cardiovascular outcome, be it microvascular (first line treatment verapamil) or due to coexisting epicardial coronary artery disease</li> <li>• May unmask arrhythmia.</li> </ul>
Rhythm monitoring	<ul style="list-style-type: none"> <li>• Indicated as part of prognostic assessment; may also shed light on symptoms</li> <li>• 24-48-hour Holter monitoring is integral to prognostic assessment.</li> <li>• Non-sustained VT is a risk factor for SCD</li> <li>• Paroxysmal atrial fibrillation is associated with increased risk of thromboembolism</li> <li>• Appropriate loop recorder/ longer-term monitoring recommended to capture an event in symptomatic cases</li> </ul>
CMR	<p>Established indications include:</p> <ul style="list-style-type: none"> <li>• Providing adjudicating images when ECG and echocardiographic findings are discordant;</li> <li>• Identifying segmental hypertrophy, particularly when localised to the anterolateral wall.</li> <li>• Evaluating the LV apex, thereby facilitating diagnosis of distal/ apical HCM and thin-walled apical aneurysms. Contrast administration improves visualisation of the apex on 2D-echocardiography, but CMR may nonetheless offer incremental value for identifying structures such as apical pouches.</li> <li>• Detection of RV involvement; &gt;40% of HCM cases in one series had maximum RV wall thickness (RVWT) <math>\geq 2</math> standard deviations above controls.</li> <li>• Diagnosis of phenotypic mimics with the aid of late gadolinium enhancement/ T1 mapping techniques</li> <li>• Quantifying extent of tissue necrosis, scarring, and LV mass regression following alcohol septal ablation.</li> </ul>

**Table 4. Guidelines for the Diagnosis of Familial Hypertrophic Cardiomyopathy** (ref 115)

<i>Major criteria</i>	<i>Minor criteria</i>
<b>Echocardiography</b>	
<p>LV wall thickness <math>\geq 13</math> mm in the anterior septum or <math>\geq 15</math> mm in the posterior septum or free wall</p> <p>Severe SAM (septal-leaflet contact)</p>	<p>LV wall thickness of 12 mm in the anterior septum or posterior wall or of 14 mm in the posterior septum or free wall</p> <p>Moderate SAM (no leaflet-septal contact).</p> <p>Redundant MV leaflets</p>
<b>Electrocardiography</b>	
<p>LVH plus repolarisation changes (Romhilt &amp; Estes)</p> <p>T wave inversion in leads I and aVL (<math>\geq 3</math>mm) (with QRS-T wave axis difference <math>\geq 30^\circ</math>), V3–V6 (<math>\geq 3</math>mm) or II and III and aVF (<math>\geq 5</math>mm)</p> <p>Abnormal Q (<math>&gt; 40</math> ms or <math>&gt;25\%</math> R wave) in at least 2 leads from II, III, aVF (in absence of left anterior hemiblock), V1–V4; or I, aVL, V5–V6</p>	<p>Complete BBB or (minor) interventricular conduction defect (in LV leads)</p> <p>Minor repolarisation changes in LV leads</p> <p>Deep S V2 (<math>&gt; 25</math>mm)</p> <p>Unexplained chest pain, dyspnoea, or syncope</p>
<p>Guidelines are applicable only to the first-degree relatives of index cases with confirmed hypertrophic cardiomyopathy, all of whom have a 50% probability of carrying the mutation.</p> <p>Diagnosis is established in the presence of:</p> <ul style="list-style-type: none"> <li>▪ One major criterion, or</li> <li>▪ Two minor echocardiographic criteria, or</li> <li>▪ One minor echocardiographic plus two minor electrocardiographic criteria.</li> </ul> <p>Other causes of LVH, e.g., athletic training and hypertension, may confound diagnosis.</p>	

**Abbreviations: LV, left ventricular; SAM, systolic anterior motion of the mitral valve;**

**MV, mitral valve; LVH, left ventricular hypertrophy; BBB, bundle branch block.**