The Cardiac Society of Australia and New Zealand

Diagnosis and Management of Hypertrophic Cardiomyopathy – Position Statement

This position statement was originally developed and co-ordinated by members of the Cardiovascular Genetics Working Group, chaired by Prof Chris Semsarian.

It has been reviewed and revised by Prof Chris Semsarian and members of the Cardiovascular Genetic Diseases Council.

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This standard of practice document briefly outlines the current approach to the diagnosis and management of hypertrophic cardiomyopathy (HCM). The supporting levels of evidence are reported in both the *American Heart Association* HCM guidelines(1) and the *European Society of Cardiology* HCM guidelines.(2) There is also a detailed recent review of HCM for further reference.(3) Since the last CSANZ HCM guidelines in 2011, the main changes relate to emerging sudden death risk factors such as the amount of myocardial fibrosis, the development of an HCM Risk Score, and more careful consideration of cascade genetic testing in asymptomatic relatives without an HCM phenotype.

1. CLINICAL CHARACTERISTICS OF HCM

1.1 Definition and prevalence

Hypertrophic cardiomyopathy (HCM) is a primary cardiac disorder characterised by hypertrophy, usually of the left ventricle, in the absence of other loading conditions, such as aortic stenosis, hypertension or thyroid disease. Although previously thought of as a rare disorder, recent population-based clinical studies suggest the prevalence of the condition to be as high as 1 in 200 in the general population (4) making HCM the commonest known cardiovascular genetic disorder known.

1.2 Clinical presentation

HCM is inherited as an autosomal dominant disorder with variable penetrance. This means affected individuals are heterozygous and offspring of affected individuals have a 50% risk of inheriting the gene mutation, with males and females equally at risk. Patients with HCM can range in presentation from minimal or no symptoms and have a benign, asymptomatic course, to the development of the

most serious complications including heart failure and sudden death. HCM is the commonest structural cause of sudden cardiac death in individuals aged less than 35 years, including competitive athletes. The pathophysiology of HCM is complex and is reflected in the diversity of clinical features. Individuals with HCM can have a variety of symptoms including chest pain, which may be typical of angina, symptoms related to pulmonary congestion, i.e. dyspnoea, fatigue, orthopnea, and paroxysmal nocturnal dyspnoea, impaired consciousness, i.e. syncopal and pre-syncopal episodes, and palpitations.(3)

1.3 Clinical diagnosis

Clinical examination features of HCM include the characteristic "jerky" rapidly rising pulse and prominent left ventricular impulse, and an apical systolic murmur, which increases with the Valsalva manoeuvre and is related to dynamic obstruction. There is frequently a fourth heart sound. The 12-lead electrocardiogram (ECG) may show abnormalities including voltage criteria for left ventricular hypertrophy, T-wave inversion and Q waves. The echocardiogram remains the investigation which most reliably confirms the diagnosis of HCM and which provides detailed information about the distribution and severity of hypertrophy, the left ventricular cavity size, assessment of left ventricular systolic and diastolic function, left ventricular outflow tract obstruction and mitral regurgitation. HCM is usually recognized by a maximal left ventricular wall thickness ≥15mm in adults (13-14 mm is considered borderline, unless there is a definite family history of HCM). Other investigations that may be helpful in confirming the diagnosis or in establishing "risk of sudden death" profile include exercise testing (with or without echocardiography or myocardial perfusion scanning), ambulatory Holter monitoring, and a history of cardiac events in other family members.

When considering the diagnosis of HCM, a number of "HCM phenocopies" may also need to be considered, particularly when the hypertrophy is more concentric rather than asymmetric. These include infiltrative disorders such as Fabry disease and amyloidosis, as well as glycgoen and lysosomal storage diseases.

Most recently, cardiac magnetic resonance (CMR) imaging has emerged as an important investigation in further defining the extent and severity of both cardiac hypertrophy and fibrosis. The diagnostic criteria for HCM remain the same as for echocardiography, i.e. maximal left ventricular wall thickness ≥15mm in adults. The main advantages of CMR imaging over echocardiography relate to quantification of fibrosis using LGE, as well as assessment of areas of the heart not as well imaged by echocardiography, namely apical HCM. Rarely, cardiac biopsies are obtained and may show the classical histopathological features of HCM, including myofibre disarray, myocyte hypertrophy and interstitial fibrosis, although such findings are usually not identified until post-mortem.

2. RISK STRATIFICATION FOR SUDDEN CARDIAC DEATH

The issue from the clinicians' perspective is how does one determine who is at highest risk of sudden death. The table below summarises the current factors considered important in evaluating which individuals with HCM are at highest risk of sudden death. Most clinicians would recommend ICD therapy if any one of the five major risk factors is present, although recent debate has focused on whether at least 2 risk factor are required. The other risk factors listed in Table 1 have been shown in studies in smaller cohorts of patients to play an incremental role in evaluating risk of sudden death, including recent early evidence that the amount of late gadolinium enhancement (LGE > 15% of left ventricular myocardium) on CMR imaging may also be an important risk factor. Clearly, many patients have some of the minor risk factors and so the decision regarding prophylactic ICD therapy is difficult. In this case, a combination of clinical judgment and the desires of the individual patient need to be considered.

Most recently, the HCM Risk Score(5) has been established which calculates risk based on a number of variables in addition to the risk factors outlined in Table 1, including LVOT gradient, left atrial size, and age at evaluation. This risk prediction model then calculates the 5-year risk of sudden cardiac death (low <4%, intermediate 4-6%, high >6%). This risk prediction model is currently undergoing validation in other independent HCM cohorts.

3. GENETIC TESTING IN HCM

3.1 HCM disease genes

Familial HCM is a genetically heterogeneous disorder, meaning a mutation in more than one gene can lead to the same condition. At least 13 causative genes have been identified to date, which primarily encode sarcomere, or sarcomere-related proteins, and include the cardiac β-myosin heavy chain (*MYH7*), myosin binding protein C (*MYBPC3*), cardiac troponin T, tropomyosin, cardiac troponin I, essential and regulatory myosin light chain, and more recently, titin and actinin-2 genes.(6) A single mutation in any of these genes will lead to HCM. Most recently, *multiple mutations* in the one individual (i.e. two or three gene mutations) have been identified, and these individuals may develop clinically more severe disease.(7, 8)

3.2 Genetic testing

Genetic testing for HCM is used to identify the disease-causing gene mutation. This genetic information can be used for cascade genetic testing in at-risk family members, and can therefore facilitate earlier management of at-risk members and avoid lifetime clinical surveillance in those family members who have a negative predictive genetic test.(9) Genetic testing may also assist in

making future reproductive decisions, since a known gene mutation in the family can be used in preimplantation genetic diagnosis (PGD), as well as in antenatal testing. Current testing suggests that screening of the 10 most common HCM-causing genes results in a gene-positive pick-up rate of 40-50%. This pick-up rate increases to 70-80% if there is a definite family history of HCM.(10) All patients need to undergo genetic counselling prior to genetic testing, and genetic testing in HCM is best undertaken in the setting of a specialised multidisciplinary clinic.(11)

4. MANAGEMENT OF HCM

4.1 Affected individuals

Major advances have been made in the management of patients with HCM in the last 5 years.(3) The clinical management of HCM however remains complex, in part due to the heterogeneous symptoms exhibited by affected individuals as well as the marked variability in the natural history of this disease. HCM can occur without symptoms, but many individuals experience some dyspnoea, angina and palpitations. The natural history of the disease is usually a gradual progression of symptoms, but in some, sudden death or severe heart failure is superimposed. Sudden death occurs most commonly in HCM either during or immediately after exercise, although death can also occur at rest.
Many treatment options are currently available for HCM patients. This ranges from no treatment; lifestyle modifications, e.g. avoiding competitive sports in all patients with HCM; use of pharmacological agents e.g. beta-blockers, calcium channel blockers, and diuretics; to surgical septal myectomy and transcoronary alcohol septal ablation of the myocardium (i.e. the creation of a limited septal infarct by direct injection of alcohol into a septal perforator artery) for individuals with significant left ventricular outflow tract obstruction with symptoms unresponsive to drug therapy. The single most important advance in the clinical management of HCM has involved the use of ICD therapy in the prevention of sudden death.(12) Recent studies indicate that treatment of individuals at highest risk of sudden death with an ICD is the most definitive form of therapy in preventing sudden death and easily surpasses empirically-based preventative strategies previously used in HCM, e.g. amiodarone and beta blockers.

4.2 Asymptomatic family members

It is strongly recommended that all first-degree relatives of an affected individual be clinically screened for HCM. As a minimum, this involves a physical examination by a cardiologist, an ECG and a transthoracic echocardiogram. CMR imaging is also emerging as an important investigation in the initial evaluation of HCM patients. The suggested time intervals for clinical screening of unaffected family members is shown in Table 2 but should be individually tailored to each person. Clinical screening in children under age 12 years is variable, and depends on clinical circumstances,

including family history. Clinical surveillance remains lifelong, although the frequency of screening is less frequent in older age groups. Screening of second-degree relatives should be decided in a family-by-family basis, and depends on a variety of factors including severity of disease in the family, outcomes from screening the first-degree relatives, the family member's desire, and clinical judgement.

4.3 Family history and genetic counselling

Genetic counselling for patients with HCM is essential. In all cases it is important that a detailed family history is taken. Particular attention to age and circumstances of a family members death, as well as retrieving any medical records or postmortem reports can provide valuable information when determining if a death was attributed to HCM. As mentioned, a family history of sudden cardiac death is a major risk factor for patients.

The inheritance of HCM should be clearly explained. This will give patients a good understanding of the risk of passing on the disorder to children and highlight the importance of clinically screening family members. If a genetic mutation is identified in the family, genetic counselling is strongly advised before family members undergo preclinical genetic testing.(13) The advantages and disadvantages of a genetic result must be fully understood before a decision about testing should be made.

5. FUTURE PERSPECTIVES

While significant advances have been made in our understanding of the pathogenesis of HCM, the genetic causes, and in the development of new approaches to diagnosis, treatment, and prevention, many clinical issues remain unresolved and will be a focus for research efforts in the coming years. These areas include defining the cause of HCM in all patients, the emergence of *genotype positive-phenotype negative* HCM patients (so-called HCM "silent gene carriers"), improving risk stratification algorithms for sudden death, further understanding the role of myocardial fibrosis in the development and progression of HCM, and developing novel therapies to treat HCM and its complications.

6. FURTHER INFORMATION

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Table 1: Risk Stratification for Sudden Cardiac Death in HCM

Major Risk Factors	Previous cardiac arrest/ventricular tachycardia (secondary prevention) Family history of premature sudden cardiac death# Left ventricular wall thickness ≥ 30 mm Previous episodes of documented NSVT (≥ 3 beats, rate ≥ 120 bpm) Unexplained syncope
Other Risk Factors	Abnormal blood pressure response to exercise* Evidence of myocardial ischaemia LVOT obstruction (≥ 30 mmHg at rest, or with provocation) Late gadolinium enhancement on CMR imaging Age at presentation (before age 21 years) Increased left atrial size

#Includes a family history of sudden cardiac death at any age if definitely caused by HCM

*Abnormal blood pressure response to exercise is defined as an increase in systolic BP <20mmHg, no rise, or a fall in BP >20mmHg during exercise, or a disproportionate fall in blood pressure immediately post-exercise.

CMR = cardiac magnetic resonance; bpm = beats per minute; LVOT = left ventricular outflow tract obstruction; NSVT = non-sustained ventricular tachycardia

Table 2: Recommended Frequency of Clinical Screening

Age (years)	Frequency of Screening (years)
0-11	Optional: unless clinical suspicion, symptoms, malignant family history of HCM
12-20	1-1.5
21-40	2-3
40+	3-5