



The Cardiac Society of Australia and New Zealand

## Guidelines for the diagnosis and management of Hypertrophic Cardiomyopathy

These guidelines were reviewed and revised by Prof Chris Semsarian and members of the Cardiac Genetic Diseases Writing Group.

The guidelines were reviewed by the Continuing Education and Recertification Committee and ratified at the CSANZ Board meeting held on Friday, 26<sup>th</sup> November 2010.

### 1. Clinical Characteristics

#### 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 0.2% (or 1 in 500) in the general population making HCM the commonest known cardiovascular genetically determined 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.

#### 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 is 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  $\geq 15$ mm in adults (13-14 mm is considered borderline, particularly so if there is a 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. Most recently, cardiac MRI is emerging as an important investigation in further defining the extent and severity of both cardiac hypertrophy and fibrosis. 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.

*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 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 are present. 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. 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.

<b>Table 1: Risk Stratification for Sudden Cardiac Death in HCM</b>	
<b>Major Risk Factors</b>	Left ventricular wall thickness $\geq 30$ mm Family history of premature sudden cardiac death Previous cardiac arrest/ventricular tachycardia Previous episodes of documented NSVT ( $\geq 3$ beats, rate $\geq 120$ bpm) Unexplained syncope
<b>Other Risk Factors</b>	Abnormal blood pressure response to exercise* Evidence of myocardial ischaemia Left ventricular outflow tract obstruction ( $\geq 30$ mmHg at rest, or with provocation)

\* Abnormal blood pressure response to exercise is defined as an increase in systolic BP  $< 20$ mmHg, no rise, or a fall in BP  $> 20$ mmHg during exercise, or a disproportionate fall in blood pressure immediately post-exercise. NSVT = nonsustained ventricular tachycardia, bpm = beats per minute.

## 2. MOLECULAR GENETICS

### 2.1 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  $\beta$ -myosin heavy chain ( $\beta$ MHC), myosin binding protein C (MyBPC), cardiac troponin T, tropomyosin, cardiac troponin I, essential and regulatory myosin light chain, and more recently, titin and actinin-2 genes. 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 appear to develop clinically more severe disease.

### 2.2 Genetic testing

Commercial genetic testing for HCM is available through several international centres. Identifying the disease-causing gene mutation can be very valuable for a family, as it can allow earlier management of at-risk members and avoid unnecessary screening of non-carriers. Genetic testing may also help to discriminate between HCM and other causes of left ventricular hypertrophy, including hypertension and “athlete’s heart.” Current testing suggests that screening of the 10 most common HCM-causing genes results in a gene-positive pick-up rate of 50-60%. In up to 5% of families, two or more disease-causing mutations are identified. All patients need to undergo genetic counselling prior to genetic testing.

## 3. MANAGEMENT

### 3.1 Affected individuals

Major advances have been made in the management of patients with HCM in the last 5 years. 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 most 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. calcium channel blockers, beta-blockers, and diuretics; to dual chamber pacing, septal myotomy-myectomy and transcatheter 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. 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.

### 3.2 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. The suggested time intervals for clinical screening of unaffected family members is shown in Table 2 but should be individually tailored to each person.

Age (yrs)	Frequency of Screening (yrs)
0-10	3-5 (optional in children < 5 yo)
11-20	1-1.5
21-30	2-3
31+	3-5

### 3.3 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 post mortem 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. The advantages and disadvantages of a genetic result must be fully understood before a decision about testing should be made.

## 4. 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 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.

## 5. FURTHER INFORMATION

### For more information:

Doolan A, Nguyen L, Semsarian C. Hypertrophic cardiomyopathy: from “heart tumour” to complex molecular genetic disorder. *Heart Lung Circ* 2004; 13:15-25.

Ingles J, Doolan A, Chiu C, Seidman JG, Seidman CE, Semsarian C. Compound and double mutations in hypertrophic cardiomyopathy patients: implications for genetic testing and counselling. *J. Med. Genet.* 2005; 42: e59.

Kelly M, Semsarian C. Multiple mutations in genetic cardiovascular disease: a marker of disease severity? *Circ. Cardiovasc. Genet.* 2009; 2: 182-190.

Lind JM, Chiu C, Semsarian C. The genetic basis of hypertrophic cardiomyopathy. *Exp. Rev. Cardiovasc. Ther.* 2006; 4(6): 927-34.

Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes M, Favale S, Piccininno M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Prevention of sudden cardiac death and selection of patients for implantable cardioverter-defibrillators in hypertrophic cardiomyopathy. *J.A.M.A.* 2007; 298: 405-12.

Maron MS, Maron BJ, Harrigan C, Buross J, Gibson CM, Olivetto I, Biller L, Lesser JR, Udelson JE, Manning WJ, Appelbaum E. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. *J Am Coll Cardiol.* 2009; 14; 54(3): 220-8.

### Useful website:

<http://www.registry.centenary.org.au/p/resources/hcm/>