Population screening for hypertrophic cardiomyopathy (HCM)

A review of the literature

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List of abbreviations

Abbreviation	Full name
ACC	American College of Cardiology
AHA	American Heart Association
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
CM	Cardiomyopathy
ECG	Electrocardiograph
ESC	European Society of Cardiology
HCM	Hypertrophic cardiomyopathy
HNOCM	Non obstructive hypertrophic cardiomyopathy
HOCM	Obstructive hypertrophic cardiomyopathy
HR	Hazard Ratio
ICD	Implantable cardioverter defibrillator
IOC	International Olympic Committee
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
NICE	National Institute for Health and Clinical Excellence
NICM	Non ischaemic cardiomyopathy
NPV	Negative predictive value
NSC	National Screening Committee, UK
NSF	National Service Framework
NYHA	New York Heart Association
PPV	Positive predictive value
RCT	Randomised controlled trial
RF	Risk factor
RXT	Randomised cross-over trial
SCD	Sudden cardiac death
s.d.	Standard Deviation
SD	Sudden death
SVT	Sustained ventricular arrhythmia
VA	Ventricular arrhythmia
VT	Ventricular tachycardia

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Executive summary

1. Background and aim

This report was commissioned by the National Screening Committee (NSC) in 2008. It updates a previous review of the evidence on screening for hypertrophic cardiomyopathy carried out for the NSC in 2003.

The aim of the project reported here was to consider the extent to which existing evidence supports the implementation of a population screening programme for HCM.

2. Review methods

A search was run from 2003 to 2008 on seven major databases (e.g.MEDLINE, EMBASE) to identify significant new evidence in relation to screening for HCM. This was supplemented by searching citation lists in existing reviews, national and international guidance on HCM, consensus statements from national and international organisations and the previous report to the NSC. Evidence was categorised and appraised using appropriate quality assessment instruments.

3. The condition

HCM is a relatively common genetic cardiac disease. It is characterised clinically by left ventricular hypertrophy in the absence of other causes and is inherited as an autosomal-dominant trait. At least 434 genetic mutations in 12 genes are implicated, nine of which encode for cardiac sarcomeric proteins.

Expression of corrupted genes varies considerably between individuals and may result in very different clinical presentation (phenotype). People may present with sudden death before developing the characteristic signs of left ventricular hypertrophy.

4. Current position on screening

Screening whole populations for HCM is generally not advocated and no current general population-based screening programmes for HCM have been identified.

In a recent autopsy-based study in England and Wales, cases of previously undiagnosed HCM accounted for only 15% of sudden cardiac deaths (SCD), with a risk of death in people aged under 55 years being around 1 per million. This would be the target population for screening.

Targeted familial screening of first-degree relatives of people found to have HCM or who suffer SCD is widely recommended and included in current NHS policy: the National Service Framework (NSF) on arrhythmias and sudden cardiac death (2005) recommended case finding in first degree relatives of victims of sudden cardiac death who died younger than 40 years of age. This population will include a proportion of cases of deaths from HCM.

Pre-participation screening of young athletes who engage in competitive or elite sports is practiced in Italy and the USA, and supported by several international organisations including FIFA and the International Olympic Committee. Notably, the British Heart Foundation is not currently supportive.

In Italy screening has been mandated in law since 1982, and in the USA it is recommended by professional medical organisations. Implementation in the USA, therefore, is ad hoc and its quality inconsistent. The programmes in Italy and USA differ in the inclusion of ECG as a part of screening (in Italy only).

5. Case definition

There is currently no clear genetic basis for case definition that provides prognostic and therapeutic value. The common case definition (left ventricular thickness ≥15mm measured with echocardiography) is difficult to apply in children, as hypertrophy usually does not develop until adolescence; fails to adults with a genetic basis for HCM but delayed LVH; may be insensitive to HCM and a in the presence of comorbidities (e.g. hypertension); may misclassify athletes due to physiological hypertrophy; and does not correlate strongly with prognosis.

6. Burden of disease

Community-based and other studies indicate that the prevalence of HCM is 0.1-0.2% and incidence 7.2-9.6 per million per year. On this basis there may be 60,000 people with HCM in England and Wales.

Estimates of their annual death rate vary by age from 1 per million in the youngest age group (<15) to 15 per million in the oldest (>75). This amounts to 170-180 deaths each year in England and Wales, with the majority of deaths (60%) in people aged over 55. There are around 16 deaths per year in people with non-obstructive HCM who are <35 year-olds and less than 40 deaths in people with HCM who were not already diagnosed.

7. Prognosis

Community-based cohort studies using echocardiography report all-cause mortality rates of 2-3% per year, with estimates of 10-years survival rates around 80-82%. However, mortality is much lower in studies which are based on people who were previously undiagnosed (around 6 per 10,000 per year).

A prospective autopsy study in England identified 453 SCDs between 1994-2003, with 6.2% attributable to HCM. The incidence of SCD from HCM is around 0.5-1 per million per year.

Athletes with HCM appear to be at increase risk of SCD, supported by the observation that SCD may occur during or just after vigorous exercise. Retrospective studies in Italy and the USA suggest that HCM is responsible for between 5.5% and 36% SCD respectively.

There is no consistent link between physical exertion and SCD in studies. Although it seems plausible that vigorous exercise might precipitate SCD it is unlikely to be the cause.

In an autopsy study in England and Wales covering 1996-1998, only 20% of SCD in previously undiagnosed people were associated with exercise and only two deaths occurred following participation in competitive sport. Italian data show similar findings.

The incidence of SCD is estimated to be 5.8 per million athlete years in Italy. The aim of any targeted screening programme involving pre-participation screening of athletes would be to reduce this very small burden in mortality.

8. The Test

Identifying high risk groups which the can be referred for effective treatment is a key function of a screening test. With respect to existing screening activities internationally, the screening test has three elements: physical examination; personal and family history; and with regard to pre-participation screening in athletes in Italy, an ECG. We identified few studies that evaluated the accuracy of the risk markers contained with these tests in a population that would be the subject of screening i.e. asymptomatic people with HCM.

Studies of potential risk markers in HCM have predominantly been carried out in symptomatic patients and their accuracy in an asymptomatic population is unknown.

Accurate diagnosis of HCM in the absence of symptoms is challenging and the Italian athlete screening programme reports the need, in a small number of cases, for intensive and prolonged investigation to reach, or rule out, a definitive diagnosis.

In relation to screening of family members for SCD, the test is whether a person is a first degree relative of someone who died suddenly before the age of 40 years. Although possession of more malignant gene such as MYH7 gene may influence prognosis in HCM, there is lack of good quality of evidence and understanding of how the presence of one or more genes may influence the risk of life-threatening arrhythmias. A current study in the Netherlands (ESCAPE) is studying genes, risk factors and prognostic associations in the longer-term. This should report in 2009.

Indirect evidence exists on family history as a risk marker from short to medium term retrospective cohort studies based in tertiary setting. Only one study was identified that investigated six major markers commonly used for risk stratification in a subgroup analysis of asymptomatic HCM patients. Three of these risk factors are included in screening testing: family history of SCD, exertional syncope and low blood pressure on exercise. An adjusted analysis in this study showed a risk ratio of SCD of between 3 and 5 in asymptomatic patients with these markers. It has also been noted that few SCD (3%) are without any risk factors.

The technical performance of the screening tests employed in the Italian screening programme for athletes has not been precisely specified. ECG appears to be associated with high specificity.

9. Treatment of HCM

The literature search did not identify randomised trials addressing the effectiveness of interventions for HCM in solely asymptomatic populations.

In relation to medication five parallel and 12 cross-over RCTs and one controlled cross-over trial were identified investigating a range of drugs and cardiac pacemakers in HCM. Studies were generally small, of short duration and poor methodological quality and were not informative in the context of the treatment of screen-detected cases of HCM.

We did not identify any systematic reviews, meta-analyses or randomised controlled trials evaluating the effect of implantable cardiac defibrillators (ICDs) in people with asymptomatic HCM.

NICE has recently reviewed its guidance on the use of ICDs and continues to support their use in conditions associated with a high risk of life-threatening arrhythmias, including HCM. Since the cost effectiveness of these devices is determined by the baseline risk of SCD as well as the effectiveness (relative risk) of treatment risk stratification is necessary to identify those screen-detected people with HCM who may be candidates. Current approaches to risk estimation are not, in our view, sufficiently well developed to achieve this routinely.

10. Evaluation of existing screening programme

There are no RCTs of existing screening programmes for HCM.

In relation to pre-participation screening in athletes, the most reliable evidence comes from the Italian screening programme. This observational evidence suggests that the incidence of SCD in athletes has fallen to below that of non athletes over the 25 years of the programme. However, the analysis was not based on cases of SCD in people with HCM who were screened compared to those who were not screened.

The Italian screening programme has developed considerably during its 25 years and is supported by a cadre of professionals (cardiologists and sports physicians) and proponents argue that the experience of screening has improved detection of important conditions other than HCM, notably Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) which has been increasingly recognised as an important cause of sudden death in Italian athletes. Overall, cardiomyopathies (including HCM) were a relatively minor cause of disqualification from competitive sports in Italy, accounting for only 7% of disqualifications (vs. 30% for hypertension and 23% for rhythm disorders).

We identified no studies which addressed the ethical or economic aspects of pre-participation screening of athletes.

11. Conclusions

Screening for hypertrophic cardiomyopathy does not currently meet the criteria proposed by the National Screening Committee.

Screening in families of affected people has previously been defined as case finding. The potential for further improvements in understanding of the genetics of the condition offers the potential for improving prognostication and treatment directed by risk of adverse outcomes, but this has yet to be realised.

General population screening is not supported by the evidence reviewed. The condition is not a major public health problem and is insufficiently well understood, with important problems relating to case definition and prognosis. The evidence base for effective treatments in asymptomatic patients is weak and inconclusive.

Pre-participation screening of athletes is appealing given the tragic nature of deaths in this population, particularly where they occur on the field of play. Although observational evidence from Italy suggests the potential for prevention of some of these deaths, the balance of benefits and harms has not yet been sufficiently well characterised. Moreover, screening of athletes seeks conditions other than HCM, and HCM may be a less important cause of sudden death than previously thought. The organisational, economic and ethical implications of implementing a pre-participation screening programme in the UK would be considerable.

11. Recommendations

1. Population-based screening for HCM should not be instituted outside the context of carefully designed research projects

2. Pre-participation screening of athletes for HCM and other causes of sudden cardiac death should not be instituted at present

3. The NSC and/or NIHR should consider commissioning further research into the potential value of screening for causes of sudden cardiac death in competitive athletes.

1. Aims of the report

The aim of the report, which was commissioned by the National Screening Committee (NSC), is to consider the extent to which existing evidence supports the institution of a population screening programme for hypertrophic cardiomyopathy.

Currently the NSC does not support population-based screening for hypertrophic cardiomyopathy (HCM). This position followed a review of the evidence by Logan in 2003, and an earlier report by the same author to the Department of Health in 1999.

The NSC considered that identifying cases through personal and family history and physical examination by a doctor, with a low threshold to proceed to further investigation, is "case-finding", rather than "screening". The Committee therefore decided there was no justification to introduce population screening for this condition.[1]

This report updates and extends the earlier Logan report by reviewing evidence published between 2003 and April 2008, in addition to that identified in the previous report.

The key principles of medical ethics – beneficence, non-maleficence, autonomy and justice – are also applicable to screening programmes.[2] For screening programmes to be ethically acceptable, there must be clear evidence that they will provide more benefit than harm to the population screened, and that they can be implemented in a just and fair manner without undermining the respect and dignity of those screened. In order to ensure this is the case, it is proposed that a number of specific criteria should be fulfilled before a screening programme is instituted. Since the original criteria were proposed by Wilson and Jüngner[3] various modifications have been proposed but all cover similar areas.[4] These are encapsulated in the UK National Screening Committee criteria and cover four broad areas: the condition, the test, the treatment and screening programme.[1]

An alternative approach to examining proposed screening programmes is to use a decision analytic approach. This is no different in underlying principle from a criteria-based approach, but has the potential advantage of emphasising the inter-relatedness of many of the criteria.[5] In such an approach, the performance of the screening test is considered explicitly alongside the potential benefits and harms that may result from the classification of screen-positive and screen-negative cases. These may include the benefits of effective treatment in preventing disease occurrence of progression, but also the harms of false positive and negative results. The decision analytic approach also allows explicit consideration of the costs and values attached to processes and outcomes within screening programmes, from health service or, more broadly, social perspectives.

However, formal decision analysis can be criticised insofar as the process of valuing outcomes may be arbitrary, and that the whole approach prioritises utilitarian ethics.[2;5] Certainly it is less adept at handling criteria derived from the ethical principles of autonomy and justice.

This review will not conduct a formal decision analysis. The decision analytical approach is briefly discussed simply to emphasise that screening criteria cannot easily be examined in isolation from one another. One cannot, for instance, sensibly judge whether or not a candidate screening test is "suitable" for a screening programme without taking account of the prevalence of the condition, the performance of subsequent diagnostic testing, the relative benefits of early versus late treatment, and the consequence of false positives in screening and diagnosis.[5]

This review addresses whether population screening for HCM meets critical and necessary conditions for population screening, as outlined by the NSC.

These are:

1. The Condition: is the natural history sufficient understood to allow use of a clear case definition?

2. The Test: can the performance of potential screening tests be characterised, and is there a defined case definition for diagnosis that can be linked to prognosis so as to guide effective treatment?

3. The Treatment: does good evidence exists that management of the condition before it is likely to present clinically confers benefit?

4. The Programme: does good evidence exist that a screening programme for the condition will confer benefits that are clinically, socially and ethically acceptable?

The report is structured as follows.

Firstly, the methods for identifying and appraising the quality of published evidence are reported. The second section considers the epidemiology of HCM, addressing the definition of cases, the evidence on prognosis and the burden of mortality which the condition places. Given the tragic and sometimes very high profile of sudden deaths in the condition, the risk of this outcome is considered in particular. The third section of the report then considers the evidence for effective interventions in HCM, and updates the previous report prepared for the NSC by Logan. Finally, we consider the evidence from Italy in support of screening of athletes prior to competition, where a national screening programme has been in place since 1982.

2. Review methods

The review has identified evidence and assessed its quality in line with the guidance published by the Centre for Reviews and Dissemination for systematic reviews.[6]

2.1.1. Identification of evidence

A systematic literature search was run from 2003 to April 2008. The aim was to identify any:

- Systematic reviews or meta-analyses,
- Randomised controlled trials (RCTs)
- Observational studies

published since the previous searches in the last review (which encompassed the periods 1966-2002 and 1966-2003). Our searches broadly addressed the questions posed in the previous section, specifically seeking studies on the:

- Case definition and natural history of HCM
- Diagnosis and prognosis of HCM, focussing on people without symptoms as this would be the focus of screening
- Effectiveness of treatments for HCM
- Evaluations of existing screening programmes elsewhere in the world

The following electronic databases were searched:

- MEDLINE
- EMBASE
- PubMed (limited to recent publications and in-process citations);
- Web of Knowledge (Sci-expanded)
- Cochrane Library (including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register)
- DARE
- NHS HTA database and other technology assessment databases.

Indexed keywords (e.g. MeSH, EMTREE) and free-text terms (e.g. “hypertrophic cardiomyopathy” and “sudden cardiac death”) were used. Previous names for this disease – hypertrophic obstructive cardiomyopathy (HOCM) and idiopathic

hypertrophic subaortic stenosis (IHSS) – were also included in the free-text terms. The exact search strategy is outlined in Appendix A.

2.1.2. Inclusion of studies

Two reviewers (JE and TM) considered the results of electronic searches for relevance to the four main NSC criteria as described above. Papers in languages other than English were excluded. The full texts of all other papers were obtained and assessed by JE for relevance.

Studies considered to be potentially relevant were coded by one researcher (JE) according to:

- Population included e.g. age range, athletes/non-athletes, family members of index cases
- Focus of the study: technical performance of screening and diagnostic tests; natural history (including studies of risk factors); effectiveness of intervention, particularly of entire screening programmes
- National and international guidelines
- Methodology used: systematic review, RCT, observational studies
- Outcomes: mortality or morbidity

Citations in retrieved studies were further examined to identify any additional studies which may have been relevant. This process was continually repeated through the review until no new material, which was considered relevant, emerged.

As population-based screening programmes seek to identify and treat pre-symptomatic cases with the aim of improving prognosis, the literature search in relation to interventions and treatments for HCM specifically aimed to include good quality evidence in people who are asymptomatic. To achieve this aim the following additional criteria were used.

1. Randomised Controlled Trials (RCTs) or Randomised Cross-over Trials (RXT)
2. HCM patient without symptoms, as defined by study authors
3. Any intervention which is controlled, be it placebo, no intervention, or anther treatment
4. Outcomes of mortality or serious morbidity

When no studies were identified which met these criteria, criterion (2) was relaxed to include studies with populations which also included people with mildly limiting symptoms of HCM. This was justified on the ground that it is not inconceivable or uncommon for people in this position to be living in the community undiagnosed.

Where this still yielded no evidence, criterion (1) was relaxed to include well-conducted controlled, observational studies.

The evidence identified from the search strategy and the application of this approach to inclusion of studies of interventions is presented in Sections 4 and 5.

2.1.3. Data extraction

Data was extracted into a bespoke database covering:

- Study design (experimental, controlled observational, observational)
- Study type (epidemiological, diagnostic, prognostic & effectiveness)
- Population / participants/ (age, gender and familial exposure to sudden unexpected death)
- Details of case definition (presence of left ventricular wall thickness (>= 15mm) in absence of other cause etc), genetic pedigree

Quantitative outcome data (mortality/survival data, morbidity (e.g. symptoms as defined by NYHA functional class I-IV) or surrogate outcomes (i.e. LV output gradient) was also recorded.

2.1.4. Appraisal of evidence

Our approach to assessing the internal validity of studies of the clinical effectiveness of treatments for HCM varied according to study design. Systematic reviews and individual RCTs were appraised using the approach published by the NHS Centre for Reviews and Dissemination (2004).[6] Cohort studies (and case-control) studies were appraised using a bespoke quality assessment instrument based on a range of sources: Levine and colleagues (1994),[7] Downs and Black (1998),[8] the NHS Centre for Reviews and Dissemination (2004)[6] and Mallen and co-workers (2006).[9]

3. Epidemiology of HCM

3.1. Disease definition

Hypertrophic cardiomyopathy is an important cause of sudden cardiac death, particularly in people aged under 35 years.[10] Such deaths are rare but devastating events which are particularly traumatic for victim's family and friends.

HCM is a genetic cardiac disease in which the heart muscle becomes pathologically hypertrophied.[11] The indispensable diagnostic characteristic is a thickened and non-dilated left ventricle in the absence of conditions that could produce the magnitude of hypertrophy present (e.g. hypertension, amyloidosis, conditions such as Fabry's disease or Marfan's syndrome).[12]

HCM is not generally an obstructive condition, although it may cause outflow obstruction and severe heart failure. In around 75% of cases, neither the thickness nor location of the hypertrophied muscle is sufficient to reduce blood flow out of the heart at rest. There are, however, a wide spectrum of morphological and clinical features.[11] Malformations of the mitral valve are common as are abnormal intramural coronary arteries with thickened walls and small lumens. At different stages of the condition such structural anomalies may cause symptoms of chest pain or angina, fatigue or exertional dyspnoea, palpitations, dizziness, syncope or congestive cardiac failure.[11;13] There may also be increased risks of myocardial ischaemia, thrombo-embolism and subacute bacterial endocarditis.[12]

The heart's conduction system may be disrupted in HCM, leading to life-threatening ventricular or supraventricular arrhythmias, atrial fibrillation and sudden, unexpected cardiac death.[14] Such a fatal outcome can occur at any age in otherwise healthy individuals, and may be the first clinical manifestation of HCM.[15] However, for most people with HCM, the disease does not cause severe problems and they are able to live a normal life.[14]

In terms of the genetics of the condition, HCM is generally inherited as an autosomal-dominant trait; that is, offspring of a genetic carrier have a 50% chance of inheriting the condition if one parent carries one copy of an aberrant gene associated with the condition. However, not all cases of HCM are inherited, with some cases resulting from sporadic mutation rather than genetic inheritance, and within the genetics of the condition there is marked variation.

At least 434 genetic mutations[16] in 12 genes are associated with HCM, nine of the genes encoding for cardiac sarcomeric proteins. These relate to the contractile, structural and regulatory functions of myofilaments of the heart muscle.[17;18] Single base mutations in three genes – β-myosin heavy chain (β-MHC), myosin binding protein C (MBPC), and cardiac troponin T (CTT) – account for a large proportion of cases.[19] In addition, multiple genetic aberrations may be present, with a greater load being associated with more adverse outcomes.[20 21] Non-sarcomere-related genes (i.e. lipid storage genes) can also contribute to the development of LVH in HCM[22] and

phenotypic expression may also be influenced by environmental factors and modifier genes such as the angiotensin converting enzyme gene.[23] [23]

Data from detailed family studies has shown that the expression of genetic mutations is heterogenous, with variable penetrance affecting the degree of hypertrophy, age of onset, LV outflow tract obstruction and premature sudden death.[23;24] The risk of these outcomes appears to vary between genetic mutations. Cardiac troponin T, and to a lesser extent β-MHC, may carry a higher risk of sudden cardiac death,[25] although this appears to vary between populations.[26] Myosin binding protein C (MBPC) is relatively benign[27] and seems to result in later onset of HCM in most populations.[28] [29]

However, even within families, let alone across populations, there is considerable phenotypic variability.[30] [31] Mutations within a single gene may vary in malignancy, significantly survival, with reports of 47% to 100% penetrance for different mutations.[32-34] Furthermore, mutations in specific sarcomere genes also vary, within some mutations unique to some populations or countries.[27;35]

These observations are generally based on large, family studies and therefore subject to tertiary referral bias. Few studies have systematically assessed the prevalence of multiple gene mutations in large, unrelated community populations to facilitate phenotype-genotype analysis.[18] [26] [22] Richard *et al*'s retrospective cross-sectional genotyping study of 197 unrelated index cases with proven LVH described considerable variation in prognosis between families.[18]

An important methodological limitation in genetic studies is that cross-sectional designs will be subject to survivor bias in that they will not include people who have already died. In relation to screening, longitudinal studies may offer the opportunity to identify asymptomatic cases with an unfavourable prognosis, such as sudden cardiac death, using risk stratification.[36] These studies are rare. One example is the ESCAPE-HCM study in the Netherlands. This multicentre prospective study is following people with three mutations in the MYBPC3 gene. However, the mutations involved appear fairly specific to the Dutch population. The study will report after 2009.[36]

In summary, genetic studies show that no single gene causes HCM; several may be involved, and these interact in different ways. Where more mutations are present, the phenotype is likely to be more severely affected,[20] including in the risk of sudden cardiac death.[21] Genetic analysis in addition to clinical diagnosis may offer advantages in identifying those with poorer prognosis,[37] and such information could be useful as a guide to intervention, but the relationships between genotype, phenotype and prognosis are not currently well understood.

3.2. Case definition and diagnosis of HCM

In adults, HCM is often defined as the presence of left ventricular wall thickness ≥15mm in the absence of other cause.[32] Others definitions specify a wall thickness of ≥13mm or greater than two standard deviations, with some adjustment for body surface area in children.[38] These definitions are often said to be easy to apply,[5;39] most commonly using two-dimensional (2D) echocardiography.[40]

More recently, echocardiographic techniques have been developed to refine diagnosis (and risk stratification) e.g. Tissue Doppler Imaging (TDI)[41] and Doppler 2D Strain velocities.[42] More modern and expensive technology such as Cardiac Magnetic Field Mapping (CMFP),[43] Positron-Emission Tomography (PET) scanning and Myocardial Imaging have also been used.[44] However, the performance of these technologies in defining the presence of HCM and, crucially, stratifying risk of outcomes so as to refine the targeting of treatment is not currently well established.

The common definition of HCM has many drawbacks and its application in practice may not be straightforward, leading to a need for further testing to confirm the diagnosis.[45] Although establishing a genetic basis for case definition has obvious appeal, as discussed in the previous section, genotypic and phenotypic heterogeneity create major challenges for the application of clinically useful diagnosis based on genetic characteristics.

The presence of LVH therefore remains central to case definition. However, this feature is associated with important diagnostic challenges particularly in relation to age.[46]

Cases may occasionally present with left ventricular hypertrophy (LVH) shortly after birth but in most LVH occurs during or soon after periods of rapid growth. Thickening of heart muscle gradually develops during childhood with detectable abnormalities usually developing during adolescence.[46] Echocardiograms are therefore seldom useful before about 10-12 years of age.[47]

HCM may remain clinically dormant for long periods of time, with symptom onset and diagnosis occurring later in life.[39] Depending on genotype, some older patients may see substantial LV thickening while in others a subsequent reduction in wall thickness may occur.[48] Therefore, the sensitivity of echocardiography will increase with age during adolescence and early adulthood and may decline in older populations.

The picture is further complicated by the relationship of LVH to the risk of morbidity and sudden cardiac death. In the latter case there is only a modest association with LVH, most reliably when LVH is >30mm and in the presence of other risk factors.[46 49] The age group with the greatest proportion of patients with cardiac hypertrophy beyond this size is that under 30 years old – one in five of patients compared to one in ten for the whole population – and are mostly asymptomatic or mildly symptomatic.[48] However, most sudden deaths occur in people with a septal wall thickness <30 mm,[49] and sudden death may be the presenting feature of HCM in the absence of any LVH.[50;51] This has led some researchers to assess other structural and functional cardiac measures in lieu of LVH.[52] Furthermore, it has been suggest that case definition of HCM using echocardiography has serious limitations, for three reasons: (1) it fails even in adults to include those with a genetic basis for HCM but no LVH; (2) false negatives may occur in people with HCM and a coexisting condition giving rise to LVH such as hypertension and (3) it focuses attention on LVH which does not correlate strongly with prognosis.[32]

3.2.1. Prevalence and incidence of HCM

There have been a range of population-based studies world-wide that have assessed prevalence and incidence of HCM, mostly in the 1980-90s. A summary of studies estimating the prevalence and incidence of HCM are shown in Appendix B. Estimates of prevalence and incidence vary by more than ten-fold; those for prevalence ranging from 0.02% to 0.23%; and for incidence from 0.24 to 3.1 per 100,000 person-years.

This considerable range reflects differences in populations, study methods and settings. Contributing factors include differences in case definition; in population genetics; and age range of sample populations. A range of different sample populations have been studied, some involving whole populations; some using a random sample from a specific community or country; and others including only cases known to health services.

Studies adopting a more selective population approach (e.g. restricting case ascertainment to health services) generally provide lower estimates of prevalence and incidence, as might be expected. Some of the variation might also be explained by the different levels of consanguinity in different countries.[53;54] In all studies, a small proportion of HCM cases might have been due to diagnostic misclassification, with LVH being attributed to HCM rather than other cause.[55] It is possible that such misclassification may over-estimate the prevalence and incidence of HCM by 1% and 2.5% respectively.[54]

Incidence and prevalence of HCM appears to fall after adolescence and then increase in middle age, with the highest rates seen in the 70s.[56] Most studies indicate the majority of cases of HCM are in people aged 40 or over.

Studies of younger populations tend to show lower prevalence and incidence for HCM, reflecting the variable course of the disease and the relationship with age discussed in the previous section. Two population-based studies of all types of cardiomyopathy in children and adolescents in Finland[57] and Australia[54] provide similar estimates of the incidence of HCM; 0.32/100,000 person-years in under 10 year olds and 0.24/100,000 under 20 year olds. Reported incidence was higher in children under one year and adolescents (which is consistent with the clinical course of the disease). Inevitably, the small number of cases means that epidemiological estimates are imprecise. Although these were population-based studies which identified HCM cases registered with health services nationally, the authors also sought cases from death certificates to increase ascertainment.

All studies showed consistently higher rates of HCM in males compared to females at all ages 70 years, by a factor of two to three.[56] However, few studies were sufficiently powered to show that these differences were statistically significant, or indeed examined the precision of their estimates.[32 54]

Evidence on whether the incidence of HCM is changing is conflicting. A number of studies throughout the 1980s and 1990s have shown an increase[53] while others indicate little or no change.[54;57 54] In the studies that saw an increase in incidence, this has been attributed to greater accuracy and use of echocardiography; increasing awareness amongst clinicians of HCM; and, in some cases, increasing levels of consanguinity in populations.[53;57]

There have been few studies in the general population seeking undiagnosed cases of HCM. Maron *et al* identified a prevalence of 0.2% in 4,111 people aged 23-35 years in Minnesota in 1987-88. This was based on six undiagnosed cases in 1,900 men and one case in 2,200 women.

3.2.2. HCM: prognosis and mortality

As noted in the introduction, the clinical picture and prognosis in HCM are extremely variable and complex. In this section, we consider the prognosis of the condition in people following diagnosis and then focus on the risk of mortality in people who are asymptomatic, the potential target of any population screening programme. Given particular concerns about the risk of mortality in undiagnosed people with HCM undertaking competitive/professional sport, this is explicitly considered in a separate subsection.

3.2.2.1. Prognosis following diagnosis

First, it is worth noting that much of the published data on the clinical course of HCM has emanated from three large centres (in the USA and Italy) often comprised of highly selected patients. In general, these study populations have been skewed towards individuals perceived to be at high-risk (the young) or those with severe symptoms requiring specialized care. Findings are therefore subject to referral and selection biases, which have distorted perceptions of the disease and its prognosis.[19;39]

Early series reported all-cause mortality in people diagnosed with HCM as around 6% per year.[19;40] These estimates were mainly based on studies conducted in tertiary referral centres.

In a systematic review covering literature up to January 2003, Elliott *et al* identified 21 studies estimating all-cause mortality and sudden death rates in people with established HCM. Studies ranged considerably in size from small to large cohorts (N=64 to N=956). Larger, more recent studies included fewer symptomatic patients (5.2% vs. 18.7%, p=0.0007), largely due to increasing case finding in affected families, with annual death rates steadying around 2-3% over the past 10 years.[58;59]

In Elliott *et al*'s own primary study – the largest and most recent – an even lower annual incidence of mortality was report at 1.0% (95% CI 0.76 to 1.26%) (deaths included resuscitated cardiac arrests and appropriate ICD discharges). Five and 10 year cumulative survival rates from all-cause mortality were estimated to be 91.2% (95% CI 89.1 to 93.3) and 80.3% (95% CI 76.2 to 84.4) respectively, in line with other studies.[60]

Similar finding have been report by Maron el al[39] who studied survival in a community-based cohort of 312 people with HCM (diagnosed by echocardiography between 1981-2001), although still identified in primary care and therefore the subject of some selection bias.[39] The probability of survival at five, 10, 15 and 20 years was 90% (95% CI, 88-92%), 82% (95% CI, 80-84%), 73% (95% CI, 70-76%), and 64% (95% CI, 60-68%) was significantly reduced compared to that of the general population (p=0.001).

The probability of survival was also related to age. Maron el al[39] found that probability of survival at five, 10 and 15 years in people ≥ 50 years did not significantly differ from all-cause mortality of an matched USA population, while for those ≤50 years old survival rates were lower.[39] In those ≥ 75 years, nearly a quarter (23%) of the cohort achieved normal life expectancy, two-thirds of people living with no, or only mildly limiting, symptoms (64%).

Although for many people HCM has a generally benign clinical course following diagnosis, patients who die from the disease usually do so in one of three ways: sudden, unexpected cardiac death, progressive heart failure and ischaemic stroke (largely embolic in origin).[40 61]

An international cohort study, which enrolled 744 consecutive and largely unselected patients and followed them over eight years showed that sudden unexpected death was relatively more common in young people with established HCM, whereas heart failure and stroke-related deaths occurred more frequently in mid-life and beyond. [61 60] The prevention of such deaths forms the basis for the use of implantable cardiac defibrillators (ICDs) which are considered in a later section of this report.

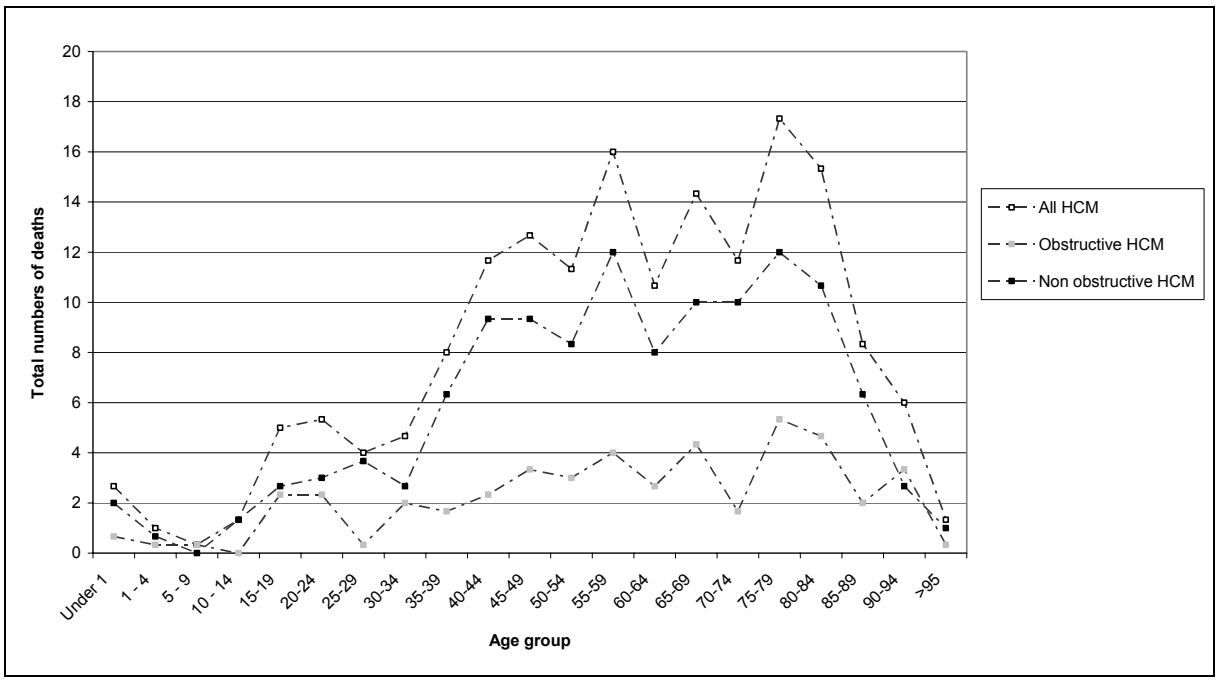
People with HCM whose mode of death is heart failure or stroke will generally be in contact with health services. However, those that die from sudden cardiac death (SCD) may well not be. As noted before, death may be the first clinical sign of the disease

3.2.3. Burden of mortality from HCM

Turning to the impact of HCM on mortality, routine statistics for England and Wales report the number of deaths from HCM as 166 in 2003, 151 in 2004, and 190 in 2005 – an average of 169 deaths per year. Of these deaths, 28% were categorised as "obstructive hypertrophic cardiomyopathy" and 72% as "other hypertrophic cardiomyopathy".[62-64] Figure 1 shows that most of these deaths occur in people older than 35 years old, with much of the increase in mortality being accounted for by obstructive cases. On average, only 14% of all HCM deaths were below the age of 35 years, and it seems likely that many of these deaths will have been due to arrhythmias.

The average number of obstructive HCM deaths is almost twice the figure quoted in the Logan report to the National Screening Committee for 1996-98 (67.5 deaths). Given that it is unlikely that the incidence of HCM is increasing in the UK population (as discussed above) this difference is likely to be due to an increased awareness of the condition.

Figure 1.Three-year averaged HCM mortality in the England and Wales, 2002-2005: ONS (I42.1 and I42.2)



3.2.4. Sudden cardiac death and HCM

Sudden cardiac death in HCM is thought to be caused by electrical instability due to structural disarray of myocytes resulting from the expression of one or more mutated sarcomere genes. This makes people with HCM prone to ventricular dysrhythmias such as ventricular tachycardia or fibrillation.[24;65] Cumulative, localised myocardial ischaemia and aortic arrhythmias which are also a feature of the disease may also increase cardiac electrical instability.

There have been four UK studies which have examined the contribution of HCM to sudden cardiac deaths.

In 1995, Bowker *et al*[66] reported the first English survey of sudden cardiac death in adults (16-64 years), defined as deaths in people with no medical history of heart disease who were last seen alive within 12 hours of death. As all sudden unexplained deaths must be reported to HM coroners, the pilot survey prospectively enrolled cases from 11 coroners, randomly select from a stratified sampled of coroner jurisdictions over a median three month period in 1991. Cause of death was certified using blood and tissue samples from the myocardium in the 65 cases identified. 89% had died of ischaemic heart disease (coronary thrombosis, myocardial ischaemia, atheroma etc). HCM was identified in only 2 cases (~3%).[66]

In 2003, Bowker *et al*[67] reported on sudden unexpected deaths in a prospective random, stratified survey of 67 coroners in 1994. A total of 1,003 cases were reported over 4 months, of which 69% (n=692) were cardiac in origin. In 95% of cases a specific cause was identified and, of these, 82.4% were due to ischaemic heart disease.

Although 32 post mortems found left ventricular hypertrophy (5.7%), detailed examination later revealed only three cases of HCM (0.5%).

Using ONS age-specific mid-year population estimates and weighting populations by caseload where there was more than one coroner per county, the authors estimated the incidence of sudden death due to cardiac causes was 10.5 per 100 000 per annum. If it is assumed that 0.5% of these deaths were due to HCM this would give a SCD rate of around 0.5 deaths per million.[67] It can also be assumed that 0.35% of all sudden cardiac or unexplained deaths were due to HCM (69%*0.5%).

In 2005, Fabre *et al*[10] reported on non-ischaemic sudden cardiac deaths in people aged >15 years old. Building on Bowker *et al*'s methods, this study prospectively identified cases returned by coroners throughout the UK between 1994 and 2003. Similarly, the cause of death was determined by histological samples, toxicology reports and clinical records. The 453 cases identified had a median age of ~31 years. A quarter had a cardiomyopathy (n=107), of which a further quarter had HCM (n=28, 26%) – 6.2% of all cases. Most cases of sudden cardiac deaths in people with HCM were males (21/28), and just over half (n=15) were aged under 35 years.

Wald *et al*[68] attempted to estimate the annual number of deaths from HCM in England and Wales between 1996-98 which had occurred in people without antemortem symptoms. They reviewed the death certificates, coroners' reports, post mortem records and contacted pathologists in order to differentiate deaths coded to the ICD9 category "other primary cardiomyopathies" (ICD9 425.4), focussing on those which indicated the cause of death as non-specific cardiomyopathy and where the death had been sudden and therefore legally required to have post mortem examination by the coroner. This group, they argued, would include cases of HCM which might have benefited from any effective screening programme.

HCM accounted for 15% of the 552 deaths during the period studied (average 184 deaths per year). Only 17% of deaths occurred in people younger than 35 years (152/184) and 60% were in people over 55 years of age.

Importantly in the context of considering population screening, most people who died suddenly from HCM had previous symptoms – only around one third of deaths occurred in people presumed to be asymptomatic before death (~65 per year). In this group, around half (37 per year, on average) were people aged less than 55 years.

Wald *et al* went on to consider the case fatality rate for HCM by combining their estimates of the number of asymptomatic deaths in England and Wales with estimates of prevalence from Maron *et al*'s study of 23-35 year olds in Minnesota.[69] Although Wald *et al* could not take account of potential differences in prevalence in those aged 35-55 years, case fatality is suggested to be low, at around 6 per 10,000 cases per annum. Wald *et al* note that this case fatality was much lower than that in studies which included cases already known to services: around 420 per 10,000 per year in tertiary centres and 110 per 10,000 per year in the general hospital population.[68]

Non UK studies showing HCM SCD as a proportion of all SCD are summarised in Table 8 in Appendix C. Estimates of HCM as a proportion of all sudden deaths in non-UK studies range from 2.8% to >8% and for SCD from 8.8%-12.5%. These figures are slightly higher than reported for England.

The largest study in USA was on military recruits and therefore this might have excluded some high risk cases of HCM where symptoms prevented them serving, leading to an under-estimate of the proportions of death overall, but perhaps more akin to an asymptomatic population which might be screened. It is also worth noting that Italy had a similar proportion of SCD due to HCM in Veneto, a region which has provided much evidence on the evaluation of pre-participation screening of athletes (see Section 5.2.3). This study produced an overall incidence rate for sudden cardiac death of 1 per 100,000 per person years.[70] [71] As only 23 death were morphological confirmed as HCM, this gave a crude estimate of the incidence of sudden cardiac death from HCM of 0.79 per million per person year.[72]

3.2.5. Sudden cardiac death and exercise

Most sudden cardiac deaths seem to occur during or just after a training session or contests in athletes participating in a variety of inotropic sporting activities, such as football of basketball. For example, studies by Maron *et al* have shown 70%[73] to 90%[74] of sudden cardiac deaths occurred during exercise. Only a third of deaths (29%) occurred during mild or recreational or sedentary activities.[73] In athletes, Corrado *et al* found 89% of SCD in Veneto, Italy occurred during exercise.[75]

However, the contribution of HCM to such deaths is not clear. A retrospective autopsy review by Fornes *et al*[76] investigated the cause of sudden cardiac death in 31 unconditioned individuals who exercise infrequently in Paris, France i.e. the study excluded elite athletes, which aroused suspicion. The proportion of SCDs due to HCM was 16.1%. Nearly all these deaths (87%) occurred whilst exercising, with running the most frequent activity.

However, in Maron *et al*'s later study of three combine cohorts believed to represent a relatively unbiased sample of clinically diagnosed cases of HCM, only one in six (16% (7/44)) collapsed during or just after vigorous physical activity, with the majority of deaths occurring while people were sedentary.[77] [61] The authors argued that this lower estimate might partly be due to widespread advice to avoid exercise given by clinicians to people diagnosed with the condition.[61]

Similar figures have been reported in a non-athletic populations by Corrado *et al*[75] in Italy, with only 14% of death occurring whilst performing mild to moderate physical exercise, and most dying while sedentary (86%). The authors here argue that the difference in proportion is due to the Italian screening programme prior to participation in competitive sport from the age of 12 years.

In England and Wales, Wald *et al*'s[68] study all HCM deaths between 1996-1998 using death certificates from the ONS. In those <55 years for which there was information on what the person was doing immediately before death, only 20% were exercising, and only 2.6% were engaged in competitive sport (2 deaths).

One consistent feature of these studies is that the number of SCDs in athletes and non-athletes was greater in men. A summary of the studies that have estimated exercise-related SCD in young athletes due to HCM or during sport related activities which identified HCM as a cause are summarised in Table 1.

Table 1. Studies of sudden cardiac deaths in young athletes or during sport related activities which identified HCM as a cause

Author / date / country	Time period	HCM (%)	HCM cases	SCD during sport	Pop[n]	Type of study	Comment
Van Camp *et al*, 1995 (USA)[78]	1983-1993	40.3%	51	136	High school and college athletes in California and North Carolina (not including deaths in PE classes)		Cause could only be ascertained in 136/160 cases, 128 using autopsy reports (80%). 126 cases were from high school and 36 college HCM cases: 50 male: 1 female. Estimated death rates were five-fold higher in males than 7.47 vs. 1.33 per million (p<0.0001) and two-fold in male college athletes than high school (14.5 vs. 6.6 per million), p<0.0001.Figures adjust to take into consideration participation in multiple sports. Annual fatality rate of 16 per year.
Maron *et al*, 1996 (USA)[73]	1985-1995	35.8%	48	134	High schools and colleges	Retrospective using clinical, eye witness, anatomic, microscopic, and toxicologic data	90% male and 44% were in African American. 90% collapsed during or immediately after a training session. 73% (115/158) of athletes were screened before participation. 68% of deaths during high aerobic sports (basket ball and football)
Basso, 1999, (Italy)[79]	1978-1993	5.5%	9	163	Population from Veneto region	Retrospective autopsy review, using clinical information and reports	163 (81.5%) of the 200 case were cardiovascular deaths. The underlying abnormality is frequently concealed and discovered only at postmortem examination
Maron *et al*, 2003 (USA) [74]	1985-2000	36%	102	286	High schools and college from 42 states	Prospective cohort with cases identified from media, informal communications and high schools and	Builds on data from the earlier study in 1996.[73] Of 585 SCD in athletes, 286 cardio-vascular deaths. HCM deaths 42 (41% white and 55%

						colleges.	(56)) African American (p=0.002). In contrast of the 1986 patients clinically identified with HCM only 158 (8% were African American (p<0.0001). HCM deaths increased with time. There were 99 male and 3 female HCM deaths.
Corrado *et al*, 2003 (Italy)[75]	1979-1999	2%	1	51	Athletes in Veneto,	Prospective cohort	This study included an athletes population after the pre-participation screening programme was introduced in 1982 is therefore is likely to be an under estimate.
Fornes, 2003 (France)[76]	1991-2001	16.1%	5	31	Individuals who exercise infrequently total population	Retrospective autopsy review	Most deaths were male (29). 27 deaths were whilst exercising, with running the most frequent activity. The 5 HCM deaths were all male aged between 13-37 years. The risk of death for SCD is 0.52 per million, (0.48 per million in males and 0.03 per million in females) population and for HCM 0.08 per million (author calculated). These are likely to under-estimates due to referral bias. Study only captured sports-related deaths considered to have aroused suspicion (not included professional athletes)

3.2.6. Risk factors for poor prognosis in HCM

Risk stratification of people with established HCM is a major part of clinical management, and key to primary prevention of adverse outcomes from this condition.

Although sudden cardiac arrest affects a small minority of the disease population, historical emphasis has understandably been on identifying high-risk sub-groups relating to sudden death and other important outcomes such as heart failure and atrial fibrillation. [17] In relation to sudden cardiac death, the identification of high risk individuals remains unresolved, with determination of risk markers hampered by heterogeneity of the condition, expression, low prevalence in clinical practice and the complexity of pathophysiological mechanisms.[19] Nevertheless, it has been possible to identify most patients at high-risk of sudden cardiac death using non-invasive clinical markers. Indeed, only about 3% of people who experience sudden cardiac death are without these major risk factors. [17 19 80]

- Strong family history of premature sudden death[81]
- Unexplained syncope, particularly when exertional
- Spontaneous sustained ventricular tachycardia (SVT) on ambulatory (Holter) ECG
- Non sustained ventricular tachycardia (NSVT) on ambulatory (Holter) ECG[81;82]
- Abnormally low exercise blood pressure, in particularly in patients < 50 years
- LV thickness ≥ 30 mm, particularly in adolescents and young adults [82-84]
- Cardiac arrest (ventricular fibrillation)

Other minor risk factors in individual patients may include:

- Atrial fibrillation
- Myocardial ischaemia
- LV outflow tract obstruction (LVOTO) (≥30 mmHg) [85 86 87 a]
- High risk mutation
- Intense (competitive) physical exertion (see later for more detailed discussion)

Other possible risk factors currently under investigation, and which may improve risk stratification include:

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[a] LVOTO only appears to be sufficient high risk maker for SCD when in the presence of other major risk factors, and risk may be exacerbated by alcohol ingestion.[87 88] Indeed, presence of LVOTO in asymptomatic people with no other risk factors may indicate a lower risk of SCD.[87]

- Coronary microvascular dysfunction[89]
- Microvolt T-wave alternans (TW)[90]
- Paced ventricular electrogram fractionation (PEFA)[91]

Non-sustained ventricular tachycardia (NSVT) appears to be the most sensitive marker of increase risk of sudden death in adults <45 years old (sensitivity=69%) and with moderately good specificity (specificity=80%). Monserrat *et al* also regard this a good predictor of sudden death in adolescents and adults (≤30 years old) in a tertiary population,[82] identifying over two-thirds of patients at risk of SCD, whilst a negative result provides good reassurance, as the negative predictive value is high, with only 3% of negative tests being false negatives. However, use of NSVT as a risk marker remains controversial because of conflicting data, with early studies [92] [93] [80] demonstrating a significant association while more recent studies have not.[94]

The positive predictive value (PPV) of the other major risk factors in HCM patients appears modest (15-28%),[80] and that for other, less well established risk markers, similar or lower.[85] [91] The accuracy of a number of risk markers still remains to be established using robust methodologies and in solely HCM populations.[90]

Risk stratification is crucial to prevention as it may increase the effectiveness of treatments to reduce the risk of sudden death. Greater accuracy in identifying high risk sub-groups could be achieved by combining two or more risks factors, but given the relatively low annual mortality rates and small size of most patient groups, this remains a significant challenge,[80] not least because of the important fact that most HCM patients (55-56%) do not manifest <u>any</u> major risk factors.[80] [75]

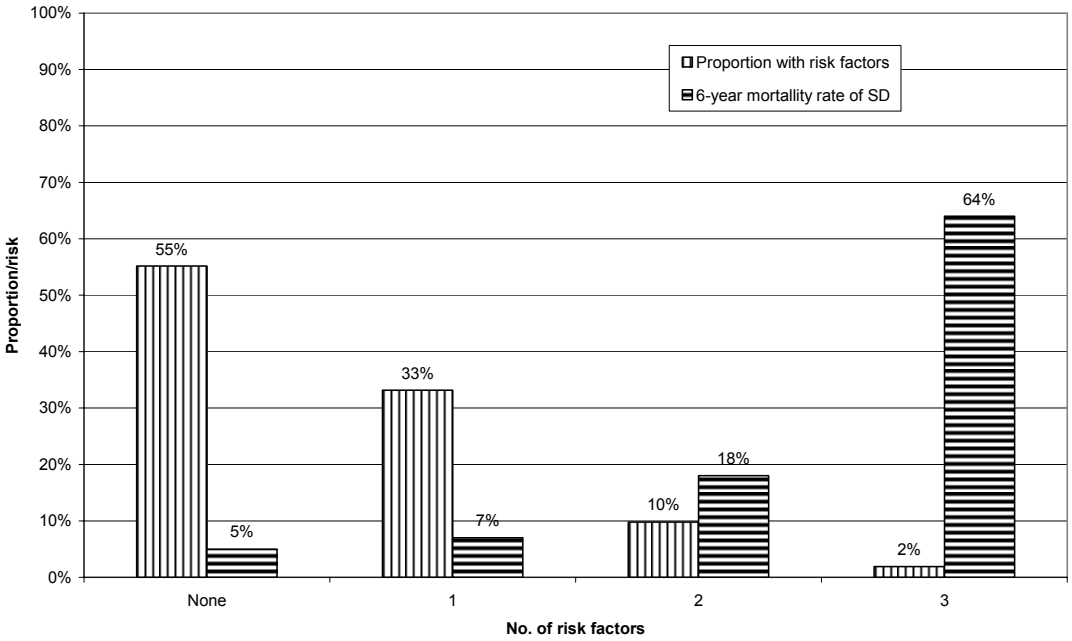
Nevertheless, there is evidence to suggest that a subset of about 10-20% HCM patients appear to be at increased risk of an adverse outcome. Elliott *et al* [80] studied five major risks in relation SD in a 368 patients with HCM (average age 37 years). The cohort was followed for an average of 3.6 years (±2.5 years). Six-year survival rate was calculated for people in each risk factor group, and was significantly reduced in those with two risks factors compared to one or none (72% (95% CI56%-88%) vs. 94% (95% CI 91%-98%)).[80] Multivariate survival analysis showed that when family history of sudden death and syncope were combined, this marker was the best predictor of sudden death. People with both these factors had a risk ratio of sudden death of 5.3 (95% CI 1.9-14.9, p=0.002) compared with those with no risk factors. This was followed by LVH ≥ 30mm with a relative risk of 2.9 (95% CI 0.7- 7.1, p=0.03). Other risk factors showed an increased relative risk but these were not statistically significant.

This study used a population from at a tertiary centre, and is therefore unrepresentative of the wider HCM population. However, when the authors' analysed the data of the 65% of patients who were NYHA Class 1 (i.e. without symptoms), all the major risk factors were significantly associated with sudden death, with similar risks ratios of SD i.e. 5.2 to 3.3.

More recently, Dimitrow and Dubiel[95] combined wall thickness and LV cavity space, together with septal curvature as markers for SCD in a retrospective, tertiary centre-based cohort study. The composite was estimated to have 91% sensitivity and 76%

specificity, with a PPV and NPV or 23% and 97% respectively.[95] More impressive results have been reported by D'Andrea *et al*, who used electro-physical markers (intra-V-Del >45ms) to predict outcome. These gave a PPV and NPV of 66.9% and 96.7% respectively.[81]

Figure 2. Proportion of patients with risk factors for SD plotted aside 6-year mortality rate of SD for groups with none to three risk factors



In general, the results of these studies are skewed by referral and survivor bias and do not specifically relate to asymptomatic people with HCM (excepting to some degree Elliott *et al*'s [80] study, where a sub-group analysis was undertaken).

Studies are not controlled and so their ability to discriminated people with asymptomatic HCM at high-risk of SD from people without HCM in a community population is not known (an important consideration when screening populations). Some of the risk markers that provide more impressive results are dependent on more invasive tests, which are more costly and probably less an appropriate and acceptable to a population based target screening programme. Importantly, most studies suggest that asymptomatic patients with no major risk factors have a low risk of sudden cardiac death.[24] In symptomatic populations, studies suggest no single risk factor (perhaps with the exception of ventricular fibrillation), can be used as a catch-all screening test for identifying people with HCM at high risk of SCD.[49] However, as Elliott *el al* demonstrate, the risk of SCD increases with each additional risk factor, with or without LVH.[49] Patients with multiple risk factors may have an estimated overall sudden death rate of 3% per year or more.[24 80 49]

It is now considered good practice to offer individuals who have two or more risk factors prophylaxis with ICD and/or drug therapy (such as amiodarone).[19;96;97] Indeed, even those individuals with one risk factors might be offered primary prevention if the physician takes into consideration any additional minor risks factors that might be present.[46]

4. The treatment and interventions for HCM

This section considers high quality evidence on the effect of interventions and treatment before on the development of symptomatic disease or significant morbidity in people. The evidence was identified using the search strategy and inclusion criteria outlined in Section 2.1.1 and 2.1.2.

Generally, randomised trials of the effective treatment may not be feasible in HCM as numbers of patients is small, event rates are low and the meaningful clinical end-point is lifetime prevention of SC, and multiple initiating mechanisms requiring different treatments may be operating. Such constraints make studying risk factors in order to target specific mechanisms more difficult to achieve.[98]

4.1. Effective interventions

4.1.1. Exercise and exercise avoidance

Although evidence is somewhat conflicting on the scale of risk, HCM is clearly a cause of sudden cardiac death in young competitive athletes and collapse in people with HCM is associated with recent exercise in a proportion of cases. Furthermore, cessation of training for at least year or more in athletes prone to ventricular tachyarrhythmias, seems to reduce the frequency and complex of such events in the majority (70%).[99]

The indirect observational evidence that exercise can induce symptoms such dyspnoea in as many as one in six (17%) asymptomatic tertiary-centre patients with HCM[44], and abnormal blood pressure in at least 11% with HCM. Both these signs are associated with an increase in risk of sudden cardiac death.[100-102] Also, that exercise may induce arrhythmias in nearly 45% of HCM patients, including atrial fibrillation (2%) and NSVT (1%)[103;104] leads credence to view that exercise avoidance is beneficial in reducing the risk of sudden death.

It is widely accepted that participation in competitive sport increases the risk of sudden death in individuals with HCM, and that patients, particularly those at higher risk, should be discouraged from strenuous exertion.[17 19 105] Others have gone further, to voice concern about the safety[104] (and value) of exercise testing in people with HCM, although this issue is still hotly contested.[103 106 107 108]

However, no trials of the effects of avoiding exercise have been cited in guidelines for HCM management. Indeed, the 2007 AHA Scientific Statement on exercise and acute cardiovascular events, which advocates a prudent approach, noted that no strategies have been adequately evaluated for their ability to reduce acute cardiovascular events, [105] and the ACC and ESC expert consensus document that there is only indirect and circumstantial evidence to support this intervention.[19]

Our literature search identified no trials of exercise avoidance in people with asymptomatic HCM. The search was broadened to include people with HCM who have mildly limiting symptoms but this too did not identify any trials.

This is perhaps not unsurprising as many cardiologists would regard such trials as unethical and impractical, as the low risk of adverse outcomes in young asymptomatic people with HCM means that very large numbers would need to be recruited to achieve acceptable power. Other challenges to such studies include defining what is meant by strenuous exercise in this context, and how this might be reliably quantified.

A broader search was therefore conducted to identify controlled observational studies in which the effect of exercise on the prognosis of HCM was evaluated.

One study was identified by Ciampi *et al.*[109] This compared the effect of isometric exercise on heart function in a small cohort of obstructive and non-obstructive HCM (n=35) with a small control group. Outcomes were limited to haemodynamic measures, and showed only a statistically significant increase in systemic vascular resistance resulting from exercise with no indication of the effect of this measure on symptoms.

As reported in Section 3.2.5, most sudden deaths in people with HCM occur at times other than when exercising, although this does not preclude a role for exercise as a precipitant of fatal arrhythmias.

A study of patients with implanted cardioverter-defibrillators (IDs) reported that only 11% of first cardiac event and appropriate discharge were related to physical exertion.[60] Although this rate may partly reflect avoidance of exercise by these patients, a more recent, larger cohort study found a similar rate of first discharge (12%) directly attributed to strenuous competitive activity.

Observational studies of pre-participation screening for athletes in the USA and Italy provide some estimates of risk. These are based on a series of assumptions (including completeness of ascertainment of death, and prevalence of HCM in athletic populations), and are therefore not precise.

The evidence base supporting the avoidance of exercise in asymptomatic patients has therefore not progressed since the last report to the NSC - estimates of the magnitude of benefit which may accrue to people with HCM from avoiding competitive sport remain speculative.

4.2. Treatment of HCM

This section discusses high quality on the effect of treatment before on the development of symptomatic disease or significant morbidity in people. The evidence was identified using the search strategy and inclusion criteria outlined in Section 2.1.1 and 2.1.2

The literature search identified no trial evidence on the effects of medical interventions in asymptomatic HCM populations.

Inclusion criteria were therefore relaxed to include studies in which asymptomatic HCM populations and mildly limiting/periodically symptomatic people (e.g. NYHA Class II).

This identified a number of systematic reviews, meta-analyses and randomised controlled or cross-over trials of a variety of interventions: various drugs, implantable

cardiac defibrillators (ICDs), dual chamber pacing, and septal interventional procedures (myectomy or percutaneous ablation). The last of these treatments are primarily used when symptoms are refractory to medication,[24;85] and are therefore not considered further.

In relation to medical therapy and ICDs, there are essentially two intervention strategies to treat HCM, depending on the expression of their condition:

- Medicinal therapy may be aimed at reducing outflow tract obstruction or suppressing arrhythmias.[19] In the screen-detected population it is likely that the latter would be more commonly used where diagnosis is accompanied with detection of ventricular arrhythmias. Other drugs, such as β-blockers, verapamil and disopyramide or sotalol, are used in order to improve the efficiency of the heart, and reduce the associated symptoms (angina, breathlessness, syncope or exercise-related hypotension).[19] This latter group of drugs is therefore likely to be rarely used in the screen-detected population, though a brief review is included here for completeness given that some cases detected by screening may already be experiencing symptoms.

- ICDs actively sense and terminate life-threatening ventricular tachyarrhythmias. They are most commonly used in people who have survived a cardiac arrest or life threatening arrhythmia (secondary prevention). Their use in asymptomatic HCM cases without such a history (primary prevention) is more controversial.[110]

4.2.1. Specific interventions

The literature search identified no randomised controlled trials (RCTs) evaluating the effect of medication in asymptomatic HCM populations.

When the inclusion criteria were relaxed to allow the study populations to include mildly limiting symptoms (i.e. NYHA Class II or equivalent), five parallel and 12 cross-over RCTs, and one controlled cross-over trial were identified.[100;111-121;121-126]

Ten[a] of these trials were reported in the previous review for the NSC on screening for HCM.[100;111-121;121-125] Two additional studies, which were published before 2003, were also identified,[123;128] and five more recent trials.[100;111;122;124 125] In two trials the NYHA functional class was not reported but the population had non-obstructive form of HCM. We assumed for the purposes of this section this population to be predominantly asymptomatic.[111;125]

The interventions involved four drug classes and two devices:

- Anti-arrhythmic agents;

- Negative inotropic drugs;

[a] One RCT from the previous report was not included as it was not in English[127]

- Angiotensin-type II receptor agonists;
- Lipid lowering agents;
- Dual chamber pacemakers;
- Implantable Cardiac Defibrillators (ICDs).

Historically, some of these drugs have been used to treat a minority of asymptomatic HCM cases,[12;19] with frequency of use increasing with the incidence of symptoms or arrhythmias. Broadly, the drug trials evaluated the following agents– β-blockers, verapamil, disopyramide, ACE inhibitors and statins – either against another drug in each class, a different class of agent or placebo.

A noticeable absence from the evidence base concerns amiodarone, which has previously been claimed to be associated with improved survival and was discussed in the last NSC review.[19]

Five trials evaluating dual chamber pacemakers were identified.

Most studies recruited patients in tertiary centres, and trials were moderately short in length; most were less than three months' duration (excluding trials of pacemakers), with some lasting days. Only two trials followed patients for a year. In total, 233 patients were studied (not including the 173 recruits in the pacemaker trials), with an average of 19 participants (mean age 42 years, range 33-63 years). Mean age in the pacemaker trials was 55 years, range 53-64.

Most trials concentrated on physiological outcomes, with none examining the effects on mortality or significant morbidity, although exercise testing and quality of life were measured in a number of studies. Data were generally not presented or analysed by NYHA class so differences in effect of medication on people with Class I and II NYHA functionality could not be evaluated.

In terms methodological quality, studies identified were generally poor. No studies reported methods of randomisation or allocation concealment to drug or placebo, and three studies reported using single blinding and one was not blinded, leaving them prone to bias.

The majority of studies were cross-over trials, which are prone to carry-over effects if the wash out period is insufficiency long. This not only dilutes any real effects but the absence of a sufficient wash out period (two drug studies and all five in DDD studies) make it difficult to determine whether there are any period effects – an important consideration in longer studies. Only one cross-over trial was designed and analysed appropriately to assess these effects.

Finally, several studies reported small differences in baseline characteristics between trial arms, but these were not adjusted for in the analysis, possibly due to the small number of participants.

The characteristics and summary results from these trials together with a critical appraisal of their methodological quality are presented in Table 9 and Table 10

respectively in Appendix D. A brief review of studies in each intervention category is discussed next.

β-blockers

There were six randomised trials and one controlled cross-over trial[100] which evaluated mainly propranolol but also practolol, and sotalol against placebo. In total, 111 (range 8-30) patients from tertiary centres were evaluated, of which 28 (25%) were asymptomatic (NYHA Class I). Study duration ranged from 30 minutes to 21 weeks. The most common outcome used (five trials) was exercise testing, others included occurrence of VT and LV functional performance.

Of the studies reporting on exercise testing, data was incomplete in one study. Three studies reported no significant effects from propranolol on this outcome. One, reasonably sized study of sotalol did report a statistically significant improvement in exercise time, but follow-up was only for 10 days. Follow-up of the cohort that benefited showed this was sustained over six months. However, the dose over this period was tripled and as there was no control group there was a possibility that improved exercise times came from dose escalation or improved fitness.

Another study compared nadolol to the Ca^{2+} antagonist verapamil in patients with mild to moderate symptoms. No significant benefit from nadolol was reported.

Calcium channel blockers

Two small studies reported on verapamil and diltiazem in 52 patients, 19 of whom were asymptomatic. Both showed no difference in the main outcomes measure, including exercise testing, between each other and for verapamil against placebo. Methodological quality was poor and follow-up was short. A third randomised cross-over study was identified evaluating diltiazem but as only 3 people had HCM out of only 10 with cardiac disease the study was not included.[129]

Angiotensin type II receptor antagonists

Two recent trials in Japan have focused on the use of angiotensin type II receptor antagonists (losartan and valsartan) to prevent the natural development of LVH in asymptomatic patients (non-obstructive HCM). The trials were undertaken following results from experimental animal studies that showed angiotensin II excretion is associated with the process of initiation and extension of myocardial hypertrophy. The Kawano *et al* trial also speculated that the angiotensin II receptor blocker valsartan may reduce the formation of cardiac fibrosis.[111]

These were fairly small trials and followed relatively older patients (mean age 56-63 years) for 12 months. Although Yamazaki *et al*, found a statistically significant reduction in LV mass from losartan, suggesting possible benefits, Kawano *et al* showed no change in LV wall thickness or ejection fraction. The findings of these studies are therefore equivocal and preliminary.

Furthermore, to be relevant to the majority of asymptomatic HCM cases more studies are required in younger patients using more relevant outcomes. That said, for the small proportion of people with asymptomatic HCM that are genetically predisposed to the development of LVH in later life, these drugs may offer a future treatment option.

Lipid lowering drugs

One RCT investigated the effect of atorvastatin against placebo. This well-conducted and reported study did not specify NYHA functional class in participants but a mean septal thickness was 16.5 (±3.5) mm and LVEF was 66.6% suggesting the population included people without symptoms. The theory behind the trial was that statins block myocyte stress signals and therefore limit LVH, as reported in other trials in animals and non-HCM patients. However, the study showed no statistically significant effect on LV mass.

Dual chamber pacemakers (DDD)

Five randomised cross-over trials were identified studying the effect DDD pacing alone or against other pacing strategies. Although the primary reason for implantation is to reduce symptoms in those refractory to medical treatment, and therefore being relevant to populations in at least NYHA Class II, it has been suggested that dual chamber pacing might result in cardiac remodelling with long-term use, and that this might reduce symptoms and risks associated with HCM. However, in general this intervention is not relevant to the population that would be the target of screening. The quality of these trials will not be discussed, although a review of their content and quality is presented in Table 9 and Table 10 in Appendix D.

Drug therapy and dual chamber pacing: discussion

The search for trials of interventions conducted here was extensive, using seven databases and register of trials. Citations in review articles were also retrieved and forward citations on any trials identified. As adverse outcomes in individuals with HCM means that studies which attempt to examine the effects of interventions on morbidity or mortality would need to be large, we believe it is unlikely that such trials would have been missed by our search strategy.

The results in most studies that compared intervention with placebo were disappointing, with few reporting significant benefits from treatment.

No trials were identified evaluating amiodarone, a commonly used drug in cases of arrhythmias in HCM and other conditions. The last NSC review reported on an influential non-randomised observational study carried out in 1985.[130] This study showed a marginally significant result in favour of amiodarone, and because it used historical controls, was appropriately regarded with some scepticism. A more recent retrospective cohort study published in 2007 supports this view.[131] This evaluated the risk of sudden death in 293 people with HCM attending a tertiary centre over a 21-year period (1980-2001), assessing the level of protection afforded by amiodarone and other drugs. Seventeen patients died suddenly or had an aborted cardiac arrest while on anti-arrhythmic drugs. A fifth (20%) of these were in patients on amiodarone (alone or with other drugs), compared 9% on verapamil, 9% on β-blockers and none on sotalol. Unfortunately statistical significance was not calculated.

The higher risk of poor outcome associated with amiodarone may have been due to confounding by baseline risk of sudden death. However, the sotalol groups had a similar risk burden to that of amiodarone, suggesting this drug may convey real benefit over amiodarone. However, it is also noteworthy that a 20 year survival analysis for those on drugs versus not on drugs did not show a statistical difference between the

groups (log rank test, p=0.08). Again, these results need interpreting with measure of caution due to the uncontrolled and retrospective nature of this study.

This is recognised in ACC/ESC Expert consensus document, which states "there is no evidence that this practice of prophylactically administering such drugs empirically to asymptomatic HCM patients to mitigate the risk for sudden cardiac death is efficacious."[19].

No RCTS of any form of intervention were identified in asymptomatic patients by our search, nor are any quoted by proponent of screening. As noted, a small number of human and animal studies have suggested that β-blockade and angiotensin-type II receptor agonists may reverse hypertrophic changes in the myocardium, but the evidence is limited and inconsistent. Similarly, it has been suggested that dual chamber pacemakers may lead to cardiac re-modelling and regression of hypertrophy but these claims remain to be substantiated, and prophylactic use in young people is questionable.

Implantable cardioverter-defibrillators (ICDs)

Since the last NSC review, ICDs have become more established as a treatment for arrhythmias causing a high risk of sudden cardiac death. This technology is therefore considered in some detail in this section.

Our literature search did not identify any systematic reviews, meta-analyses or randomised controlled trials evaluating the effect of implanting ICDs solely in people with asymptomatic HCM.

Eleven uncontrolled observational studies were identified which evaluated ICDs in people with HCM.[65;132-141] All study populations included the ICDs implanted for primary and secondary prevention. In general, candidates for secondary prevention had survived a cardiac arrest or sustained spontaneous ventricular tachycardia resulting in haemodynamic compromise. Insertion for primary prevention was in cases thought to be at particularly high risk due to previous syncope, VT or adverse family history. Although ICDs were the intervention of interest, in five studies some of the devices also incorporated a dual chamber pacemaker. In addition, the majority of study participants were also on medication, suggesting the populations were predominantly symptomatic.

Children and/or adolescents were the focus of the study population in three studies of ICDs,[137-139] but in one study there was only three HCM cases in the study population, [138] and in another, the device used at the time did not routinely allow reliable classification of reasons for discharge.[139] These latter two studies were therefore excluded.

Five studies appeared to report overlapping study populations. For example, the largest and most recent study by Maron *et al*[135] included or appeared to include people from previous studies, namely, Maron *et al*[134], Jayatilleke *et al*[132], Marín *et al*[65] and Woo *et al*.[140]

In general, studies also varied slightly in how they measured outcomes, the number and nature of clinical indicators used for candidate selection and mean length of follow-up (range: 20-44 months). Studies also varied considerably in size and quality

of analysis and reporting. The findings of few studies were adjusted for confounders when making comparisons and it was not always clear how those who were handled in analyses. Confidence intervals were not provided with some studies. In some studies outcomes were not assessed solely from retrieved data retrieved from the ICD – symptom reports or stressful/emotional circumstances were used to judge the appropriateness of ICD discharges. Only one study mentioned blind assessment of outcomes.

A summary of these studies and their results is presented in Table 11 and a critical review of their quality is presented in Table 12 in Appendix E.

We consider the studies by Maron el al,[135] Marín *et al*[65] and Kaski *et al*[137] in more depth as these were the largest and most recent identified, and were well conducted, reported and analysed. Together, Maron el al[135] and Marín *et al*[65] represent about 80% of all study participants reported in the literature reviewed. Kaski *et al*'s study specifically focuses on implantation in children and adolescents with HCM (≤ 16 years) – a time during which hypertrophy often develops – and is also the largest and most recent study in this population.

Maron *et al*'s report on a multicentre study of ICDs implanted between 1986 and 2003 in 506 people attending 42 institutions in the USA, Europe and Australia, who were followed until April 2005.[135] This study included 150 patients from an earlier investigation by Maron *et al* in 2000,[134] which was reviewed in detail in the 2003 NSC report. Maron *et al*'s earlier study was reported to have influenced the use of ICDs in the management of people with HCM at risk of SCD, including primary prevention,[134] increasing the use of ICD implants in the USA and Europe.[142]

In Maron *et al*'s more recent study, 76% of 383 people with HCM had ICDs fitted for primary prevention. Just over half of these people (52%) were asymptomatic and a third (33%) had mildly limiting symptoms (NYHA Class II). Of the 103 people who experienced one or more appropriate discharge(s), half (51) were in the primary prevention group i.e. 13% (51/383) of the primary prevention cohort experienced potentially life-saving intervention.

The intervention rate in the primary prevention group was 3.6% per year (95% CI, 2.7%-4.8%), a third of that of the secondary prevention group. The cumulative probability of discharge at 5 years was 17% (s.d. 2%), just over a quarter of patients (27%) having a cumulative probability of a first discharge after this period. This was significantly less than for secondary prevention. Similar results were also reported in a study by Begley *et al.*[133] There was no difference in discharge rates between men and women (p=0.6), nor association between age at implantation and risk of appropriate discharge (p=0.64).

This study also sought correlations between discharge rates and established risk factors. In the primary prevention group, nearly half of patients had no or only one risk factor. Analysis showed that discharge rates were independent of the number of risk factors present. Unfortunately, one important risk factor associated with SCD – hypotension on exercise – was not investigated.

There was only one sudden cardiac death amongst the 39 fatalities which occurred during follow-up. This was in an asymptomatic 21-year-old man with non-obstructive HCM, whose ICD malfunctioned.

Although the results suggest the use of ICD for primary prevention appears effective in terminating potentially life-threatening arrhythmias, the intervention had some negative consequences. Major infection and haemorrhage/thrombosis was reported in 3.8% and 1.6% of patients respectively. Device dysfunction was reported in 6.7% of implants. A quarter of patients received inappropriate shocks – although evidence suggests these will affect quality of life only if their frequency is greater than four inappropriate discharges.[143]

Studies in children are rare and generally small in size. Many of those which have investigated ICD implantation in children have focused on populations with a range of cardiac diseases and have few cases of HCM.[138;139]

Only one study was identified in our search - Kaski *et al*. This included 160 consecutively referrals to a UK tertiary paediatric centre. ICDs were implanted in 22 children, 16 of which also included dual-chamber pacemakers. In 17 children the indication was for primary prevention, among whom mean age at implantation was 14 years (range 0.3-15), the majority having no or only mildly limiting symptoms. Only one person had an appropriate discharge in the primary prevention group (4.5%). The annual discharge rate in this group was 4.1%, with a 5-year shock free survival of 93.3%, which was not statistically significant. The mean time to first appropriate shock was 3.3 months. The short follow-up of a potentially life-long intervention and the relatively rate outcome rates meant it is difficult to determine whether the effectiveness of ICDs was better, equivalent or worse than that in older cohorts. A common limitation of ICD studies in children, including the two discussed here, is differentiation between supraventricular and ventricular tachycardias, which may lead to overestimation of appropriate discharge rates.[138]

ICDs: discussion

Comparison of studies of mortality in HCM with trials of ICDs suggests the technology may be effective in preventing sudden cardiac death.[40] However, studies of ICD have a number of limitations.

First, although the majority of the implants were for primary prevention not all implantees were asymptomatic at the time of device insertion. Of the four studies that reported the proportion of the cohort that were NYHA functional Class I, the proportion of asymptomatic cases ranged from 50 to 65%. It is therefore not clear how generalisable the apparent benefits in these patients from tertiary referral centres would be to the largely asymptomatic, community-based population which would be identified by screening.[144] The criteria for implantation in most studies was the presence of two or more risk factors. Indeed, Maron *et al*'s study challenges this criteria as no association was found between outcome and the number of risk factors.

Second, follow-up in most studies was fairly short and therefore the number of appropriate discharge small. Survival rates are only reported in one study.[133] Long-term studies of people younger than 35 years are important, as this group is a large recipient of ICDs.[65;142] Most studies therefore use appropriate ICD discharge as a surrogate measure, that the first appropriate discharge, on detection of a significant VT

or VF, has been life-saving. However, results from the DEFINITE trial has shown that discharge rates may not be a reliable proxy for sudden death, with episodes of NSVT frequently terminating spontaneously in non-ischemic cardiomyopathy.[145]

Survival rates or cumulative discharge rates on their own, however, require careful interpretation as these studies have no control group. Any comparator will need to have similar age, sex and ethnic populations to ensure that any differences seen can be attributed solely to the implant and not to underlying differences in other factors which might influence survival. For example, in Elliott *et al*'s study,[40] which included a review of 21 survival studies of patients with HCM (with and without ICDs), the six most recent studies show that populations which included people with ICDs had worse annual death rates than those which did not.

Furthermore, using studies which have measured survival rates from diagnosis as a comparator will be misleading due to lead time bias which is likely to influence results in favour of ICDs. Comparator studies may also lead to "length time" bias. Studies of ICD may not contain those at highest risk of SCD, as these individuals may have died before being offered an ICD. This effect can be seen in the results presented in Elliott *et al*'s[40] study in which the HCM database at St George's Hospital (1998-2002) was analysed.[a] This revealed a 44% improvement in annual survival rate from 0.5% (95%CI, 0.36%-0.64%) to 0.9% (95%CI, 0.64%-1.16%) when moving from calculations based on time from diagnosis to those made from time from initial evaluation.

The lack of good quality evidence relating to ICDs in HCM is not surprising given the low prevalence of the condition in cardiologic practice, its heterogeneous expression, and the relative novelty of ICDs.[135] Despite these caveats there has been considerable accrual of evidence on the effectiveness of ICDs in the last 10 years, and devices are widely used to treat people with conductive heart disorders, including ischaemic and non-ischaemic cardiomyopathies which increase the risk of sudden death.[142] Given that the underlying mechanism precipitating death (VT/VF) may be similar to that in HCM, it does not seem unreasonable to consider the findings of this research as potentially relevant to the HCM population.

At least 10 RCTs comparing the prophylactic use of ICDs to conventional medication or placebo, can be identified in the literature.[146] Unfortunately none have specifically identified HCM cases and analysed them as a sub-group. Desai *et al*[147] have meta-analysed data arising from five primary prevention trials, which involved patients with non-ischaemic dilated cardiomyopathies – CAT[148] AMIOVIRT,[149] DEFINTIE,[150] SCD-Heft[151] and COMPANION[152] – pooling the results of 1854 patients. The analysis, which used a fixed effects model, suggested a 31% reduction in all-cause mortality in those receiving an ICD (in many cases with biventricular pacemakers) compared to those on medical therapy. The reduction in sudden was not calculated, but cohort studies suggest it may be nearly half of this.[19]

The evidence shows, that primary prevention in high risk patients with history of VT, including those with LVEF ≤35% and mild to moderate symptoms (NYHA Class II or

[a] This study could not be used as a comparator as it did not present outcomes for patients who were in NYHA Classes I or II, or separate primary from secondary prevention in the analysis.

III) reduces the risk of sudden cardiac death.[153] However, the AMIOVIRT trial[149] was the only study to include significant numbers of patients who were asymptomatic or had mildly limiting symptoms (NYHA Class I: 16%; Class II: 63%). This trial did not show a statistically significant benefit of ICD versus amiodarone after four year's follow-up (p=0.8).

Therefore the effectiveness and appropriate selection of patients for this therapy is controversial and remains unresolved.[135 154] and more research is needed to define groups at sufficiently high risk of sudden death to make the intervention appropriate.[96] For primary prevention in HCM this is a particular challenge given difficulty in risk in this heterogenous disease.[142] In practice, HCM patients in the USA are frequently offered ICDs even when only one major risk factor is present, with the exception of hypotension during exercise.[142]

In the UK the use of ICDs increased from 3.8 to 20 per million population between in 1995 and 2002.[110] In 2000, the National Institute for Clinical Excellence (NICE) supported the use of ICDs, with acceptable indications being extended in a 2006 review of its guidance.[155] Much of the evidence reviewed for NICE was based on trials following MIs and in heart failure. The economic analysis considered by NICE clearly demonstrated the relationship between device cost and baseline risk of sudden death, as well as the improvement in relative risk from ICD shown in the various trials reviewed.

Given the price to the NHS assumed by NICE for an ICD in 2006 (£16,250) and an estimate for the relative risk of sudden death from ICDs compared to medical therapy of 0.43, the baseline risk of sudden cardiac death at which ICD would be considered cost effective (at £30,000 per QALY) was 13-20%.

Despite limitations in the evidence base reviewed, and no specific consideration of HCM, the guidance issued to the NHS includes "familial cardiac condition with a high risk of sudden death, including … hypertrophic cardiomyopathy", an indication which was maintained from the original 2000 guidance. This relatively open indication further underscores the importance, for cost effectiveness, as well as clinical effectiveness, of more accurate stratification of risk in HCM in order to ensure that the use of ICDs in the context of a screening programme might be considered an efficient use of NHS resources since the average risk of sudden death in HCM may well be lower than the figures suggested by NICE.

Treatments for HCM; summary

The evidence base in support of effective drug or device interventions in the population of people with HCM who might be identified by screening remains limited and inconclusive. The critical determinant of effectiveness and cost effectiveness (particularly for ICDs) is quantification of the baseline risk of life-threatening cardiac events and sudden cardiac death. This remains extremely challenging in the context of HCM generally, and is likely to be more so in the population of sufferers that might be identified by population screening.

5. Approaches to screening for HCM

Screening whole populations for HCM has not generally been advocated. Nor, with one exception, has it apparently been studied. Japanese school children resident in Tokyo's Adachi Ward (population ~650,000) were screened twice for conditions predisposing to cardiac arrhythmias, including HCM, at 6-7 years and 12-13 years of age between 1981-1992.[156] The prevention of sudden death by this strategy was more limited than expected.[157]

This section therefore describes approaches to familial screening (case finding) for HCM and to screening of athletes. In both cases, current arrangements are described first, followed by a discussion of the evidence base.

In the case of screening for HCM in athletes, it is clear that the principle concern that screening may address is the risk of sudden death in young adults, for which HCM is the underlying condition. Therefore, we discuss the contribution of HCM to sudden cardiac death, the precise quantification of which is difficult but is important in considering the potential value of a screening programme directed specifically at the identification of cases of HCM.

5.1. Targeted familial screening (case finding)

The rationale for targeted familial screening is the fact that first-degree relatives of people with HCM have 50% chance of inheriting a mutant gene from one of their parents.[36] In rare instances, both patents may carry a mutant gene in which case all siblings will express the mutant genes.

Familial screening of first-degree relatives of people found to have HCM or who suffer sudden cardiac death is widely recommended, even among those who doubt the value of screening in other high risk groups or populations.[158] However, the criteria relating to the age at which screening should be undertaken, the interval between screening, and age criteria for the index case (e.g. <40 years) varies internationally.

Where familial screening is undertaken, the process involves initial discussion of presymptomatic molecular and cardiological diagnosis. Evaluation may then be carried out using personal and family history, physical examination, 12 lead ECG and 2D echocardiography in order to assess risk factors for sudden cardiac death.[19;36;38]

In terms of case finding in relatives of people with HCM which has not resulted in sudden death, the Hypertrophic Cardiomyopathy Association and the British Heart Foundation have recommended that families of cases should be screened. More precise recommendations have been made by bodies in the USA for family screening for HCM. Table 2 summarises different national and professional organisations and charitable bodies' positions on familial case finding for HCM.

Genetic familial screening is still in its infancy. In the Netherland, familial screening for cardiac arrhythmias including HCM has been advocated since 1996 (although frequently not performed). Since 2003, a limited DNA testing service has allowed

surveillance of MYBPC3 gene mutation carriers, even though it is not part of the formal screening programme.[36] [157] The efficacy of this screening strategy has not yet been established.

The ESCAPE study in the Netherlands is seeking to identify how genotype and risk factors are associated with morbidity, mortality and sudden cardiac death, with a view to determining which is the best strategy in to identify high risk groups in that country. This study will report after 2009. However, the study is focusing on several mutations which are reported to be unique to that population. Thus, the generalisability of the study's findings to the population of England and Wales are likely to be of less value.

Table 2: Positions on familial screening for HCM

Organisation/country	Population	Interval	Screening test/approach	Year
ACC/ESC Expert Consensus Document on HCM[19]	First degree relatives of index cases and other family members	Annually (12-18 year olds) Adults (every 5 years)	If DNA analysis not available: Personal and family history Physical examination 12 lead ECG Echocardiography	2003
Hypertrophic Cardiomyopathy Association, USA[159]	First degree relatives	Annually (12-18 months) (12-20 year olds) >25 years (every 5 years) Not children (except if multiple deaths in family or competitive athlete)	12 lead ECG Echocardiography Visit to cardiologist	2008
Hypertrophic Cardiomyopathy Association, UK	Families of cases should be screened	None given	None identified from a search of their website	2008
British Heart Foundation[160]	Families of cases should be screened	None given	None identified from a search of their website	2008

In Australia in 2006, the National Horizon Scanning Unit argued that there was limited evidence to support the screening of family members for genetic mutations implicated in HCM, and recommended the technology be monitored before making this a recommendation.[161]

In the UK, the position for familial screening following a case of sudden death is more clearly defined and is supported in NHS policy. In 2005, the National Service Framework (NSF)[162] on arrhythmias and sudden cardiac death recommended referral of first degree relatives of victims of sudden cardiac death who die below the age of 40 years for cardiological evaluation. As discussed in Section 4, it also states that those considered at high risk of sudden cardiac death should be considered for preventative treatment with ICDs.[162] This may include people with HCM. This follows a recommendation in NICE Clinical Guideline 5 in 2003 which supported the use of

ICDs in people with familial cardiac conditions such as HCM, for the purposes of primary prevention.[163]

5.2. Screening of athletes

5.2.1. International positions on screening in athletes

Table 3 summarises different organisations' positions on screening for HCM in relation to participation in competitive sports.

In the USA in 1996, the American Heart Association (AHA) consensus panel stated that pre-participation cardiovascular screening for young competitive athletes is justified on ethical, legal and medical grounds. In 2005, the consensus panel revised its recommendations, calling for a standard pre-screening protocol across the USA, to include family and personal history and physical examination by a doctor, with a low threshold for proceeding to further investigation.[164]

At the same time in Europe, a working group of the European Society of Cardiology (ESC) issued a consensus statement on pre-participation screening of young competitive athletes, calling for a common European protocol. The ESC also reinforced the 1996 AHA consensus panel's support for pre-participation medical clearance of all young competitive athletes involved in organised sports programmes.[165]

The ESC's statement drew heavily on the Italian experience of pre-participation screening. Italy has had a national programme in place since 1982, mandated in law. The "European protocol" is supported by the International Olympic Committee, although it is made clear that participation is voluntary.

The European and American protocols differ. The former recommends the use of 12-lead ECG in screening, in addition to personal and family history and physical examination. This is held to improve sensitivity of screening and improve cost-effectiveness.[164-167] The AHA does not include ECG as part of screening.

Since 2006, the International Federation of Football Associations (FIFA) has also required pre-participation cardiovascular screening on all football players participating in the World Cup championship.[168] The International Cycling Union has also made pre-participation screening obligatory and includes ECG and echocardiography in screening.[166]

Although no direct evidence of benefit exists, the consensus of the medical community, expressed through AHA and ECS scientific statements and guidance, is that young (and master) athletes with HCM should avoid exposure to competitive sport.[19;96;169] Whether individuals with unequivocal evidence of HCM should be restricted or disqualified from competition, as happens in Italy, is not always clear in international sports federations/committees' guidance. Given that the prognosis of HCM varies considerably, such advice has been questioned.[170;171] In the UK, the Hypertrophic Cardiomyopathy Association and National Sports Medicine Institute announced a project to assess the feasibility of screening for

Table 3. Summary of national and professional organisation's positions on screening of athletes.

Organisation/country	Population	Interval	Screening test/approach	Year
Italy	Mandatory screening of all young prospective competitive high school and college athletes	Annual or biannually (12-35 years)	Personal family history Physical examination 12 lead electrocardiogram (ECG)	1982
Lausanne recommendation, International Olympic Committee[166]	All participants at beginning of competitive athletes up to age 35.	Prior to Olympics games, every 2 years	Personal and family history Physical examination 12 lead ECG	2004
FIFA	International Professional Footballers	Prior to 2006 FIFA World Cup Germany	Physical examination ECG and Echocardiograms	2006
European Society of Cardiology[165]	Young competitive athletes involved in organised sports	Start at between 12-14 years old, and every 2 years thereafter	Personal and family history Physical examination 12 lead ECG	2005
American Heart Association (36th Bethesda Conference)[164;167]	High school and college athletes	2-4 years	Personal and family history Physical examination	2005
Hypertrophic Cardiomyopathy Association, USA	Young children (optional)	None given	Personal and family history Physical examination	2008
British Heart Foundation[160]	Not supported	Not stated	Not applicable	2008

athletes aged 15-30 for cardiac disease in 1994.[98] However, a citation search did not identify any follow up studies or any publications arising from this pilot.

5.2.2. Implementation of screening of athletes

A systematic review of pre-participation screening protocols in 2006 noted that existing protocols may not be implemented in full.[166] Some are inadequate for cardiovascular evaluation and contain four or fewer items recommended by the AHA. All protocols included medical history and a physical examination, and in some cases various diagnostic tests.[166]

The person recommended to carry out screening is also variable, with some places allowing non-physicians to conduct examination. Bille *et al* concluded that the application of protocols was so poor that the usefulness of pre-participation screening is questionable.[166] This supports the findings of an earlier survey of USA National Collegiate Athletic Association members between 1995 and 1997, which reported that while 97% required pre-participation screening, only a quarter (26%) had what they described as an "adequate" programme, including at least 9 of the 12 elements recommended by the AHA.[172] A survey of guidelines for pre-participation screening in US high schools reported that 43 of 51 States require screening, but only 17 were regarded adequate in light of AHA recommendations.[173] These finding have been accompanied by calls for standardisation of pre-participation screening to improve effectiveness.[77]

Pre-participation screening involving ECG and echocardiography is also occurring independently and in an *ad hoc* fashion in many sports organisations and clubs. Elite athletes are often subject to periodic health screening, not only to protect their health but also the organisation or club's investments. Whether such screening practices comply with the IOC's Lausanne Recommendations is not known.[171]

5.2.3. Evidence base for pre-participation screening of athletes

No prospective trials of pre-participation screening in athletes were identified in the literature registered on research databases. However, we identified a number of observational studies evaluating the effectiveness of pre-participation screening in reducing the number of sudden cardiac deaths.

Before moving on to describe the most significant of these studies, this section considers several issues of importance in relation to HCM and the risk of sudden death in athletes.

5.2.3.1. HCM and sudden cardiac death in athletes

A range of challenges exist in considering the risk of sudden cardiac death from any cause in athletes, and more specifically risk contingent on the presence of HCM. These are important when considering the potential value of pre-participation screening, and include the impact on the diagnosis of HCM of the physiological impact of training on cardiac morphology and electrophysiology; the significance of history of

syncope; and the importance of exercise as a risk factor for precipitating sudden cardiac death in athletes.

Definition of left ventricular hypertrophy

The use of septal wall thickness as a risk marker for sudden death in athletes is confounded by the observation that competitive training may increase the septal wall thickness to a degree similar to that seen in people with HCM. There is therefore an overlap between physiological changes in this population due to intense training, particularly in dynamic sports such as rowing or cycling, and pathological conditions such as HCM, myocarditis and arrhythmogenic right ventricular cardiomyopathy (ARVC).[174] This is what Maron calls the "Grey zone" and is an important challenge in the diagnosis and management potential cases arising in the context of screening.[175]

For example, an echocardiographic study of 442 (306 males) elite British athletes between 1994-2001 revealed that 2.5% (n=11) male athletes presented with a wall thickness ≥13mm, which would be commensurate with a diagnosis of HCM.[176] This concurs with an earlier Italian study by Pelliccia *et al* in 1991,[177] but is higher than a more recent study by Pelliccia *et al* which reports 1%.[45] The upper limits of wall thickness in British athletes was 16mm, slightly greater than the normal athletic heart (14 mm) and in world class professional cyclists evaluated in another study.[178]

"Athlete's heart" clearly has implications for the sensitivity, specificity and accuracy of using wall thickness in the echocardiographic diagnosis of HCM. However, in relation to extreme LVH ≥30mm, a major risk factor for SCD, such hypertrophy was not reported as within the normal range of the athletic heart. This still raises the question of whether increased LVH raises the risk in athletes.

Maron *et al*[175] has specified additional criteria to differentiate HCM from the athlete's heart. In additional to unusual LVH and family history of HCM they identified the following markers:[175]

- LV cavity <45 mm (positive)
- LA enlargement >55 mm (negative)
- Bizarre ECG patterns (positive)
- Abnormal filling (positive)
- Female gender (positive)
- Reduced thickness with deconditioning (within three months) (negative)
- Max VO_2 >45ml/kg/min or >110% predicted (assessed on exercise) (positive)

More recent studies have suggested that 2D echocardiographic strain profiles[179] and Doppler tissue imaging may be used to differentiated athletes' heart from hypertrophy in HCM. This is based on the finding of a small, controlled cross-sectional studies, although positive and negative predictive values have not been calculated.[52]

Syncope

Syncope, considered to be a risk factor for sudden cardiac death, may be less predictive of HCM or subsequent cardiac events in athletes. Colvicchi *et al*[180] found that 6.2% of young athletes had syncopal episodes, but in only 1.3% were these *during* exercise – the majority of episodes were due to post-exertional postural hypotension. In this study, syncope without other cardiovascular abnormalities was not associated with adverse outcomes.[180]

ECG findings

As noted, protocols for pre-participation screening from the AHA and other bodies differ in respect of the inclusion of ECG.

The interpretation of the ECG in athletes may be difficult. Physiologic adaptation and remodelling of the heart in response to fitness training in elite athletes results in abnormal ECG patterns in about 40% of athletes, some resembling cardiac disease.[181;182] Trained athletes without structural heart disease are also subject to arrhythmias and conduction alterations.

Maron *et al* studied the prognostic significance of ECG findings in a prospective study of 355 competitive athletes.[181] Athletes were investigated either (a) because of palpitations, (b) the presence of >3 premature ventricular depolarization on rest on 12-lead ECG, or (c) both. The authors found arrhythmias were usually not associated with underlying cardiovascular abnormalities, which were only detected in 7% (n=26) of young athletes, and conclude that such arrhythmias, without clear cardiovascular abnormalities, are not clinically significant and do not warrant disqualification from competitive sports.

In a more recent study, Pelliccia *et al*, using the Italian national database of pre-participation screening of athletes, investigated the predictive value of ECG as part of assessment where no structural abnormalities were present. Eighty-one elite athletes in whom initial ECG findings were markedly abnormal but not accompanied by any structural cardiac abnormality formed the "exposed" group in this historical cohort study (0.6% of the whole population of tested athletes). This group was matched with 229 similar athletes without initial ECG abnormalities. Follow up was for a mean of 9 years (s.d.±7). Eleven (14%) of the "exposed" group were diagnosed with a cardiac disorder during follow up, including one case of ARVC which was missed at initial screening (and who died suddenly one year later) and three cases of HCM (one of whom suffered a cardiac arrest). In contrast, only four of the 229 control athletes were diagnosed with a cardiac condition during follow up, none of which was cardiomyopathy.

5.2.4. Sudden cardiac death in athletes and the contribution of HCM

Given the lack of direct evidence that stopping people taking parting in sport reduces the risk of sudden death, a key question must be to what extent participation in sport raises the risk of death in people with HCM.

There is no simple answer and estimates of risk must come with important caveats relating to individuals participating in multiple sports; recreation activity versus competitive sport; methods of case ascertainment; and selection bias due to different populations.[78] Therefore the precise frequency with which sudden death occurs in young athletes (those under 35 years of age) remains unclear and estimates available from the literature vary.

In Minnesota, the annual incidence of sudden death due to undiagnosed cardiovascular disease is reported to be about 1 in 200,000 high-school athletes participating in organized sports. However, such data are limited, and the magnitude of this public health problem may be considerably underestimated.[181]

Most series show the majority of person who die suddenly during sports activity did not have a history of pre-existing cardiovascular symptoms: sudden death was their presenting symptoms.[78] An exception is Corrado *et al*'s early study in Italy, in which 45% of young athletes had a history of symptoms.[183]

The risk of sudden non-traumatic death occurring during or within one hour of participation in sport has been estimated in a number of studies. Van Camp *et al*[78] in the USA estimated the risk in school and college students involved in competitive sports between 1983-93 as being 7.47 per million for males and 1.33 per million for females.[78] The difference between sexes was significant ($p<0.0001$).[78] The accuracy of this figure is dependent on the completeness of reporting and in this study extraordinary efforts were made to locate all cases from multiple sources. In males, 40.3% (50/124 cases where information was available) deaths were attributed to HCM, making the risk of sudden death from HCM 3.01 per million young male athletes. The highest risk was in male college athletes (aged 18-24) at 14.50 per million college athlete, statistically more than twice that of high school athletes (aged 13-18) ($p<0.0001$).

In Italy, Corrado *et al* estimated the number of SCD death in the Veneto region of Italy in athletes in competitive sports between 1979-1981, importantly *before* the Italian national screening programme was introduced.[75] Fourteen deaths were identified, of which five were cardiomyopathies, giving an incidence of 1.50 (0.21-2.78) per 100,000 athlete years.[75]

In Maron's study follow up study of 286 sudden deaths from CVD between 1985 and 2000, 36% were due to HCM. Deaths occurred in athletes participating in a variety of sporting activities and most occurred during or just after a training session or contests. However, 29% (82 athletes) occurred during mild or recreational or sedentary activities.[74]

Several autopsy-based studies have also documented that sudden cardiac deaths in young competitive athletes (<35 years) may be due to a range of diseases but that HCM is a major underlying condition.[181] Studies of sudden death in athletes are unavoidably influenced by selection biases and other limitations in absence of a systematic national register.[77] Nevertheless, in the USA, Maron *et al*[73] estimate that HCM accounts for a quarter of all 26.4% sudden cardiac deaths, and if non traumatic injury (i.e. commotio cordis) and drug abuse are excluded this rises to 36.3%.

Van Camp *et al*'s earlier study, which used the same database including many of the same athletes, produced an even greater estimate for the contribution of HCM of 51%.[78]

Finally, Corrado *et al*'s prospective study in the Veneto region of Italy produced a much lower estimate with 1 out of 55 sudden death in athletes (12-35 years) due to HCM (1.8%).[72] This study is important in that it sought to estimate population-based estimates prospectively and separated HCM from ARVC. The risk of sudden cardiac death among athletes and non-athletes was investigated by cause and gender.

Table 4. Causes of sudden cardiac death in young athletes

	Van Camp *et al*[78]	**Maron *et al*[73]**	**Corrado *et al*[72]**
N deaths	100	134	55
Age range of cases	13 - 24	12 - 40	12 - 35
HCM	51	36	1
Probable HCM	5	10	-
Coronary anomalies	18	23	9
Valvular and subvalvular aortic stenosis	8	4	-
Possible myocarditis	7	3	5
Dilated and non-specific cardiomyopathy	7	3	1
Atherosclerosis / coronary artery disease	3	2	10
Aortic dissection / rupture	2	5	1
ARVC	1	3	11
Myocardial scarring	-	3	-
Mitral valve prolapse	1	2	6
Other congenital abnormalities	-	1.5	-
Long QT syndrome	-	0.5	1
Wolff-Parkinson White Syndrome	1	-	1
Cardiac conduction disease	-	-	3
Cardiac sarcoidosis	-	0.5	-
Coronary artery aneurysm	1	-	-
Normal heart at post mortem	7	2	1
Pulmonary embolism	-	-	1

Mortality from sudden cardiac death was higher in athletes than non-athletes (RR=2.1, C.I. 1.5 to 2.8) indicating the potential for strenuous activity to act as a trigger for underlying cardiovascular disease. The commonest underlying cause of death among athletes was arrhythmogenic right ventricular cardiomyopathy (ARVC), which accounted for 12 of the 55 deaths (22%). The risk of sudden death from ARVC was

higher than that for HCM in athletes, and second only to coronary artery disease, with RR=5.4 (2.5 to 11.2).

The three major series that have estimated exercise-related SCD in young athletes are summarised in Table 4 (cited in Thompson *et al*[105]). This shows the different relative contributions of HCM and ARVC to sudden deaths between studies. The reasons for this different pattern of cause are uncertain but may relate to differences in diagnostic criteria, or changes in ascertainment over time. Alternatively, the role of ARVC may have become relatively more important in Italy since the institution of the national pre-participation screening programme.

5.2.4.1. Studies of screening programmes in athletes

It is important to note that the purpose of pre-participation screening of athletes is principally to prevent "athletic field death".[165] In this section we review studies evaluating the impact of pre-participation screening programmes with particular focus on HCM.

The evidence base for screening in athletes predominantly comes from four observational studies of the Italian experience of pre-participation screening in 12 to 35 year olds taking part in competitive sport, which was made statutory in 1982. This followed the institution of screening in the Veneto region more than a decade previously. Three of the studies reported in this section were published by Corrado *et al*, based in Padua.[71;75;184] The fourth examines the inclusion of ECG in the Italian pre-participation screening protocol, and was based in a specialist referral centre in Rome.[45]

In 1998, Corrado *et al*[184] first reported on a population-based, cohort study of the screening programme in the Veneto region, in the North East of Italy (including the cities of Venice, Padua and Verona), between 1979 and 1996. This study was discussed at some length in the review by Logan (2003).[5]

In brief, the authors screened 33,735 young athletes for a range of cardiac problems, using a combination of ECG, personal and family history and physical examination. They identified 22 people with HCM (giving a prevalence of 0.0652%) and stopped them playing sport, none of whom died during this period. During the same period, out of a population <35 of the 2,009,600 people, 16 died suddenly and unexpectedly (immediately or within six hours of onset of symptoms) as a result of HCM.[184]

The authors use the difference in proportion of sudden cardiac mortality due to HCM in the athlete and non-athlete groups, and similar prevalences of HCM in non-athletes in Italy and USA, to argue that this indirectly demonstrates the effectiveness of screening. However, these claims are not substantiated by the analysis, as the study did not compare the risk of unexpected death amongst those with HCM in the screened and unscreened populations.

If we assume the same prevalence of HCM in the general population as amongst screened athletes then we would expect 1,311 people (0.065% x 2,009,600) with HCM in the general population. We can then compare the risk of death amongst the 22 people prevented from competing in sport (0/22=0%) and the risk amongst the general

population of 1.22%. (16/1311). There is no statistical significant difference between rates in the two groups (χ^2 test: p=0.7; Fisher exact test p=1.0; Wilson comparison of two independent proportions with continuity correction: 95% CIs overlap (1.22% (0.7% – 2.0%) versus 0% (0.4% – 18.5%)).

Furthermore, such an analysis does not take into consideration the differences in the two populations, such as the differing demographic profiles (age and sex) and lifestyles which could confound the analysis.

In their second paper, published in 2003, Corrado *et al* reported on pre-participation screening in the same region between 1979 and 1999.[71] Three hundred cases of sudden death were reported, 31 more than in the previous study. During the extra three year period, one additional person (an athlete) was reported to have died suddenly from HCM. Therefore, 1.8% deaths in athletes were due to HCM compared to 8.9% in non athletes. The average incidence of sudden death among athletes was one death in 2,368,590 observation years, an incidence of 0.42 per million athlete-years.

In comparison, there were 22 sudden deaths among non-athletes due to HCM over 26,750,010 observations years (29,118,600-2,368,590), giving an incidence of 0.82 per million non-athlete years i.e. around twice that experienced by athletes. The author presented values from a Poisson multivariate regression analysis which adjusted for possible differences between populations (although potential confounders which were included in the model were poorly specified). Taking account of covariates generally increased the statistically significant of relative risks for sudden cardiac death between athletic and non-athletic populations. However, this analysis considered all causes of sudden death as the study's focus was on whether sports activity increases risk of sudden death, rather than quantifying the contribution of identification of HCM from screening.

The study period also bridged the introduction of the national screening programme. It is not clear how and whether the number of athlete years before 1982 were calculate or whether they were included in the final figures. Potentially, this could artificially increase the number of deaths in the non-athletic population. Finally, an inappropriate analysis was undertaken as the risk in people with HCM was not assessed.

In their most recent paper (2006),[75] Corrado *et al* describe trends in the incidence sudden death before and after the adoption of national pre-participation screening of athletes, and compares these to trends of sudden cardiac death among the non-athlete population in the same region. This study is particularly important as the most recent study from this screening programme which focuses explicitly on the effectiveness of case identification and associated outcomes.

Corrado *et al* (2006) reports mortality trends in three periods: pre-screening (1979-1981); early screening (1982-1992); and late screening (1993-2004). Trends in mortality are compared with that for non-athletes over the same period. The incidence of sudden cardiac death in both groups was obtained from the Veneto Regional Registry of Juvenile Sudden Death. Sudden death is defined as occurring instantaneously or within one hour of collapse. Deaths were considered cardiac in origin where post-mortem examination identified the primary cause within the heart or great vessels without evidence of a non-cardiac cause.

The Veneto Registry has been prospectively collecting information on deaths in people aged under 35 years since 1979. The hospitals which provide data to the Registry cover 95% of the population of Veneto.

The denominator for incidence rates in athletic and non-athletic populations was drawn from the Italian national decennial censuses carried out in 1971-2001, with linear interpolation between censuses used to estimate individual year populations for Veneto. This is different from the approach taken in the UK to estimate individual mid-year populations, in which birth, death and migration data are used.

Although there is likely to be a numerator-denominator problem in the incidence rates calculated by Corrado *et al* (2006), and some inaccuracy in the annual population estimates, these factors are unlikely to introduce substantial bias in the comparison of mortality rates between the athletic and non-athletic populations.

As stated, the analysis compares pre-, early and late screening periods. Table 5 shows the results for total deaths in athletes and non-athletes and for those attributed to cardiomyopathies. Note that cardiomyopathies in this study includes HCM, dilated cardiomyopathy, restrictive cardiomyopathy and ARVC.

Table 5: Incidence of sudden cardiac death in young people in the Veneto Region of Italy

	Pre-screening (1979-1981)		**Early Screening (1982-1992)**		**Late Screening (1993-2004)**		
	N	**Rate[a]**	**N**	**Rate[a]**	**N**	**Rate[a]**	**RR[b]**
Athletes							
Total deaths	14	4.19 (1.78-7.59)	29	2.35 (1.94-2.75)	12	0.87 (0.46-1.28)	0.21 (0.09-0.48)
Cardiomyopathy deaths	5	1.5 (0.21-2.78)	7	0.57 (0.26-0.87)	2	0.15 (0-0.36)	0.10 (0.01-0.59)
Non-athletes							
Total deaths	29	0.77 (0.26-1.26)	110	0.79 (0.69-0.88)	126	0.81 (0.68-0.94)	1.05 (0.69-1.64)
Cardiomyopathy deaths	8	0.21 (0.10-0.33)	35	0.25 (0.17-0.33)	40	0.26 (0.19-0.33)	1.21 (0.56-2.99)

a: rate per 100,000 population per year

b: relative risk for late screening vs. pre-screening periods

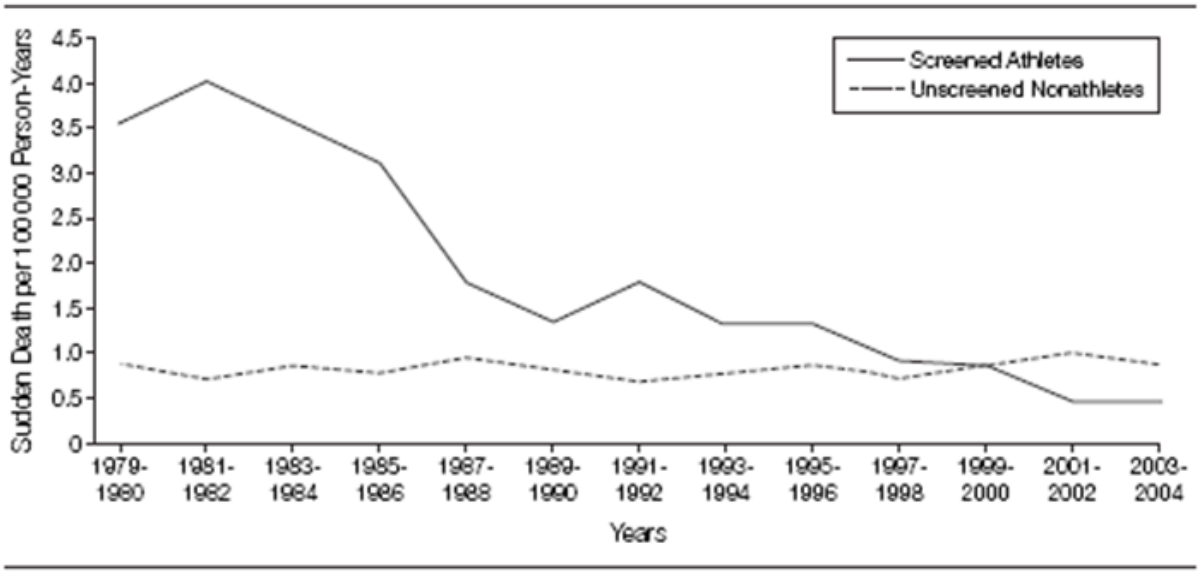
Table 5 shows a decrease in screening death rates after the institution of screening, of 44% and 63% for the early and late screening periods respectively. For individual year estimates, the average annual incidence of sudden death among decreased 89% from 1979/80 to 2003/04 (test for trend: $p < 0.001$).

In contrast, over the course of the study, sudden cardiac death in non-athletes remained steady over the equivalent period (see Figure 3).

During the study period, 55 athletes died, of whom 24 had been screened and 10 had been referred for more intensive investigation (including echocardiography, Holter monitoring, and exercise testing). Unfortunately, the Corrado *et al* (2006) study did not calculate the technical performance of the screening and diagnostic tests undertaken in the Veneto region, although this was not the primary purpose of the study.

It is difficult to identify the contribution of the diagnosis of HCM, as opposed to other causes of death, to the fall in mortality shown. However, it seems clear that ARVC was a particularly important cause of sudden death in this cohort, and that much of the reduction in mortality was due to its identification. The mortality rate from this condition declined by 84% (p=0.02) from the pre- to late screening periods. By inference from the reported AVRC-specific mortality rate for the late period (0.15 per 100,000 per year) all cardiomyopathy deaths in the late period were due to this cause.

Figure 3: Annual incidence rates of sudden cardiovascular death in screened competitive athletes and unscreened non athletes aged 12 to 35 years in the Veneto region of Italy (1979-2004)



A sub-study is also reported in Corrado *et al*, based on the experience of disqualifying athletes from athletics at the Centre for Sports Medicine in Padua. This centre screened 11% (n=42,386) of the region's athletes, and referred 9% of these for further investigation after positive screening tests, which led to disqualification from athletics in 2% (n=879) of the total screened.

Over the total screening period in Padua, 60 people with cardiomyopathy were disqualified from athletic competition, 30 of whom had HCM. The number of cases of cardiomyopathy disqualified doubled in the late compared to early period, although the number of cases of HCM remained constant (14 and 16 in the early and late periods respectively). In other words, an average of less than two cases per year were identified.

The number of cases of ARVC, on the other hand, increased significantly from 2 (0.4% of all disqualifications) to 14 (3.3%) across the two periods (p=0.004), which

accounts for much of the increase in identification of cardiomyopathies in the screened population. Corrado *et al* go on to attribute much of the change in mortality shown as a result of screening to the dramatic decrease in mortality from ARVC, asserting that sports physicians and cardiologists have become more expert at recognising the condition.

It is also suggested that the number of cases of HCM identified has remained stable because of its greater acceptance and ease of diagnosis, and note that none of the athletes disqualified from competitive athletics experienced sudden cardiac death. However, no details are available on whether these disqualified athletes were treated for HCM or whether they continued with recreational sport. This raises the important issue of exercise as a risk factor for sudden death in cases of HCM, as reviewed in 3.2.5. While exercise appears to be important as a potential precipitant of death, estimates of the risk associated with exercise are difficult to obtain and available information, based on history of cases of sudden death, varies considerably and may be confounded by the impact of screening and by reporting biases.

Cardiomyopathy was a relatively minor cause of disqualification, being the reason in only 6.8% of cases, compared to rhythm disorders and hypertension (39% and 23% respectively).

Corrado *et al* suggest that the decrease in mortality from sudden cardiac death can be attributed to the adoption of pre-participation for athletes for three reasons:

1. Co-incident timing between the decline of sudden cardiac death in athletes and the implementation of the national screening programme.

2. Most of the reduction in incidence in sudden cardiac death was due to fewer cases of cardiomyopathies, and was accompanied by an increase in the proportion of athletes who were identified and disqualified from competition because of this group of conditions.

3. The incidence of sudden cardiac death did not change in the unscreened population.

Although the evidence from the Italian screening programme could be construed as that of a "natural experiment", there are a number of caveats that need to be considered in respect of screening for HCM.

These are now discussed with reference to the above three points.

1. That the gradual decline in incidence of sudden cardiac deaths in athletes was mainly due to cardiomyopathies might be explained by changes in the demography of male and female athletes throughout the 1980s and 1990s, with a greater proportion of women participating in competitive sports. As evidence suggests that women have lower sudden cardiac death rates than men, the gradual fall in HCM may be confounded. The number of male and female participants was not reported by Corrado *et al*. Behavioural factors might also be at play, with changes to training regimes and diet as part of the increasing professionalisation of sport over the study period. Both these factors may make a difference to physical fitness and how the athletic heart responds in the competitive

environment. Such biases are inherent weakness of observational studies but can be addressed to some degree in the analysis, as was the case in Corrado *et al*'s earlier study[71] which controlled for gender in a multivariate analysis. .

2. The reduction in cardiomyopathy is mainly due to ARVC not HCM *per se*. With the advent of screening a formal training programme was institutionalised, with clinical personnel able to take professional qualifications in screening and the interpretation of ECGs. Thus, the fall in CM and increase of ARVC may have been due to improved diagnosis and differentiation between ARVC and HCM, as noted above.

3. While the incidence of sudden cardiac death in non-athletes acts as a proxy control group compared to the screened athletes, it may be a poor proxy. None of the studies reviewed here have carried out the crucial analysis with respect to the value of screening for HCM i.e. comparing the incidence of sudden cardiac death in people with HCM who have been screened with those who have not.

These three points, particularly the last, weaken the conclusions drawn by Italian researchers and others (i.e. the AHA and ESC) with respect to screening for HCM using the Italian protocol. Interestingly, in the USA the inclusion of ECGs in the Italian protocol remains controversial as this investigation is considered too expensive.

The final study which we have included in this section also describes the Italian experience of screening. In 2006, Pelliccia *et al* reported on their experience of screening 4,485 members of Italian national sporting teams in a specialist centre in Rome between 1990 and 1998. About 500 such elite athletes per year are selected for detailed evaluation in this specialist centre, with a protocol which routinely includes echocardiography. Since all referrals to this centre were in athletes already declared eligible for competition, the study was able only to investigate the specificity of screening, using echocardiography and, in some cases, additional tests (cardiac MRI and genetic testing) over a prolonged period.

Echocardiography identified 41 athletes with LVH (0.9%) and 12 athletes with undiagnosed other cardiac anomalies (ARVC, Marfan's Syndrome, myocarditis and valvular disorders). Thirty seven of the 41 athletes with LVH were judged to have "athlete's heart" and four considered to be in the "grey zone", as Pelliccia has termed the overlap between LVH and HCM in athletes. These cases were extensively investigated over 8 and 9 years follow-up respectively. One was eventually diagnosed as a definite case of HCM after genetic testing and the other as a possible case after developing NSVT and echocardiographical and arteriographic changes. It is not clear whether these athletes had continued in international sports during follow-up.

The study suggests that ECG may be an effective element in the Italian pre-participation screening protocol, at least insofar as it appears to have high sensitivity (around 99%). However, as noted by Pelliccia *et al*, sensitivity was not calculable in this study, which was confined to screen-negative cases.

6. Discussion

Although further research has been published since the last report considered by the National Screening Committee, it is difficult to conclude that the evidence base which might support the establishment of screening programmes for HCM has changed substantially.

Since the last NSC report the HCM Associations in the USA and UK, the British Heart Foundation have called for investigation of family members of diagnosed cases of HCM. The NSC's position on targeted screening in families has been that this constitutes case finding and not population screening. It may therefore be unnecessary to consider this issue further. However, it is worth noting that none of the organisations which support familial screening for HCM have suggested evidence-based approaches to this service and our searches identified no studies exploring this using scientific methods. The same is true of screening in cases of sudden cardiac death, which will include a proportion of cases of HCM, although this is already supported in NHS policy.

Understanding of the genetics of HCM has continued to increase over the last five years, and the genetic basis for the condition is now better understood. However, phenotypic variability is such that the identification of causal genetic aberrations cannot yet guide treatment decisions, nor usefully provide the basis for prognostic advice in affected families. This position may change on the publication of ongoing research, at which time further policy consideration may be warranted.

Screening of athletes prior to participation in competitive sports remains a high profile issue for policy-makers, particularly given the high profile and tragic nature of deaths occurring in such people, and the (perhaps increasing) value placed by society on sporting achievement. Since the last NSC report there have been several further studies of the Italian experience of pre-participation screening, which still dominates the available evidence base.

The Italian programme seeks a range of potential causes of sudden cardiac death associated with exercise, carrying out screening using personal and family history, medical examination and ECG. The programme has apparently influenced the development of positive recommendations for screening by a range of organisations, notably FIFA and the IOC. The British Heart Foundation, however, does not currently support such screening.

The most important recent study from Italian researchers has examined trends in death rates among athletes and non-athletes in one region of Italy, based on a comprehensive registry of deaths among people aged less than 35 years. While this shows that the incidence of sudden cardiac deaths has fallen since screening was instituted in Italy, the study has some important potential weaknesses. In particular, the incidence of sudden death among people with HCM who were screened, and those who were not, remains unknown.

Interestingly, the Italian experience seems to suggest a growing role for ARVC in the incidence of sudden cardiac deaths in athletes. What is not clear is whether this is a consequence of people with HCM at high risk of sudden death being removed from the pool of athletes, or improvements in diagnosis of ARVC. Overall, HCM has been a

relatively minor cause of disqualification from competitive sport in Italy, with rhythm disorders and hypertension being more important. Of course, whether disqualification results in a meaningful reduction in risk of death depends on the role of exercise in the aetiology of sudden cardiac death and the effectiveness of advice to reduce strenuous exercise.

The precise contribution of exercise to sudden cardiac death in HCM remains unclear, partly because of the small number of cases which occur. In the general population, exercise seems associated with SCD in 15-20% of cases and some evidence suggests this figure is higher in athletes, although methodological challenges make a firm conclusion on this issue difficult. It seems likely that in some cases of HCM exercise may act as a precipitant of fatal arrhythmias. The identification of such cases remains currently very difficult. We found no evidence which addressed the effectiveness of exercise avoidance in HCM and it seems unlikely, given the small number of cases, that high quality studies will be carried out in future.

The Italian screening experience is informative in a number of further respects. The programme has been developed over 25 years and is carried out by interested cardiologists and sports physicians. Formal training programmes have been developed to establish and support this cadre of professionals. It seems likely that there are, as a consequence, currently more of these professionals in Italy than in the UK. The organisational impacts of adopting a screening programme in the UK have been beyond the scope of this review but would need to be considered in any further work.

The Italian screening programme also demonstrates the difficulty in reaching a diagnosis of HCM in athletes due to the overlap between pathological and physiological cardiac morphology in this population. In the large regional study of screening referred to above, half of the deaths which occurred were in athletes who had been passed as eligible for competition, some following further testing. While the proportion of cases of HCM in this group is not reported, and the technical performance of the screening and diagnostic elements of the Italian screening programme have not been specified in detail, this underlines the fact that no screening or diagnostic test is perfect.

The harms of pre-participation screening have not been discussed in the literature we have reviewed. These are worthy of some consideration given uncertainty over the precise risk which athletes who might be identified as screen-positive would face. With the growing professionalisation of sports, disqualification without good evidence of significant risk in the individual concerned may have significant impacts, including implications for further employment and insurance cover.

The ongoing debate about the role of ECG and, perhaps, echocardiography in the screening and diagnosis of athletes highlights uncertainty regarding the value of tests for risk of SCD in general, which also apply to HCM. It is, however, clear that in some cases intensive investigation of screen positive cases and those whose diagnostic test results are equivocal may be necessary before a diagnosis can be reached or confidently ruled out. The economic consequences of such activities have received almost no attention in the literature, beyond the view from the AHA that ECG screening is not justified as a use of resources.

Considering the potential for screening of HCM more widely, it should be noted that there are probably around 60,000 people with the condition in the UK but less than 40 deaths amongst those who were not diagnosed at the time of death[68]. Annual mortality from HCM seems to be around 1-2%, and in most cases (particularly those with older age at onset), life expectancy is not reduced. In athletes, the most comprehensive UK study identified only two deaths after competitive sport and the rate of sudden cardiac deaths from other studies appears very small indeed, at around 4-6 per million athlete-years. Since HCM causes only a minority of these deaths (with risk difficult to stratify), and given the lack of evidence on the performance of screening and diagnostic tests and the effectiveness of treatments, the potential for HCM screening to make a substantial impact remains limited and speculative. This must be balanced against the fiscal and organisational resources which would be required to implement an effective screening programme in the UK.

Turning to the NSC's criteria for the adoption of screening programmes, HCM does not fare well, although as noted at the beginning of this report, criterion-based assessment of screening has limitations. While HCM is a relatively common cause of sudden cardiac death, such deaths are rare. The public health importance of the condition in this respect relates to the apparently increased risk of such deaths in younger patients and the high profile of deaths in competitive sportsmen and women. The consistent finding that such deaths are more common in men than women should be noted.

The epidemiology and natural history of HCM is incompletely understood, particularly with respect to the risk of sudden death. Epidemiological studies based on tertiary referral centres unsurprisingly appear to report higher deaths than community based studies. The most relevant recent UK study by (Wald *et al*) [68] provides some reassurance on case fatality in undiagnosed HCM, at about 6 per 10,000 per year.

As a genetic condition, there is currently no prospect for primary prevention of the disease itself. Furthermore, understanding of the relationship between genotype and phenotype is currently such that affected people cannot easily be advised of the likely natural history of their condition or potential implications for their offspring. Genetic testing for HCM is currently still at a relatively early stage of development, although some relevant research is underway. We found no studies investigating the acceptability of genetic screening in families affected by HCM.

In the context of familial screening of cases of HCM and pre-participation screening of athletes, personal and family history, medical examination, ECG and echocardiography are the screening and initial investigative tests generally employed. It is noteworthy that organisations supporting such screening have not defined, or agreed upon, appropriate further diagnostic investigations.

The evidence for effective treatments which can be instituted following early diagnosis with the expectation of improved outcomes is limited. We found no studies in solely asymptomatic populations with HCM and risk stratification of cases remains unresolved. Studies of drug and device interventions have predominantly been carried out in people with symptoms of heart failure or history of arrhythmias and the preventive potential for benefits of these technologies in a screen-detected population is therefore not clear. Given the demonstration of the important relationship between

risk of sudden death, effectiveness, device price and cost effectiveness, risk stratification in cases of HCM is of obvious importance.

The organisational implications of instituting a screening programme for athletes prior to competition have already been highlighted.

There is no randomised controlled evidence to inform policy on screening in HCM, although the rarity of the condition makes such studies unlikely to be feasible. Available evidence comes from observational studies and there have been no previous decision analytic studies or evaluations structured around internationally accepted criteria. The potential harms, and costs, of screening programmes have not been considered in the literature we have reviewed.

7. Conclusion

The case supporting population screening for HCM is weak. Despite concerns about high profile and very tragic deaths among athletes, and an increasing level of support for screening of athletes from international organisations, the evidence supporting such screening is not conclusive. Furthermore, the organisational implications for the NHS may be considerable, suggesting a very cautious approach should be adopted in addressing this issue.

8. Recommendations

1. Population-based screening for HCM should not be instituted outside the context of carefully designed research projects

2. Pre-participation screening of athletes for HCM and other causes of sudden cardiac death should not be instituted at present

3. The NSC and/or NIHR should consider commissioning further research into the potential value of screening for causes of sudden cardiac death in competitive athletes.

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Appendicies

Appendix A

Hypertrophic Cardiomyopathy Screening Searches – February 2008

The primary search was conducted on 05/02/08 on the databases list below using the terms and combinations to identify any relevant experiment or observational studies.

The same search strategy was re-run 03/04/08 on all databases below between 2003 to date and Cochrane 2008 issue 1 using the terms: familial or genet$3 or cardiomyop$6 and sudden cardiac death or Death-Sudden-Cardiac#.DE.

Cochrane CDSR, CENTRAL, HTA 2008/1

#1 MeSH descriptor Cardiomyopathy, Hypertrophic explode all trees

#2 (hypertroph*) NEAR (cardiomyopath* OR stenosis OR septal OR asymmetric)

#3 (stenosis) NEAR (muscular OR sub ADJ aort* OR sub-aort* or subaort*)

#4 HOCM OR IHSS or HCM

#5 (#1 OR #2 OR #3 OR #4)

#6 MeSH descriptor Death, Sudden, Cardiac explode tree 2

#7 (#6 AND (hypertroph* or MeSH descriptor Hypertrophy, Left Ventricular, this term only)

#8 #5 or #7

Medline on Dialog Datastar 1996-date [05/02/08]

LIMITS: YEARS 2003-date, English language

1. SEARCH: HYPERTROPHIC-CARDIOMYOPATHY#.DE. OR HYPERTROPHIC-CARDIOMYOPATHY#.DE.

2. SEARCH: HYPERTROPH$4 NEAR (CARDIOMYOPATH$4 OR STENOSIS OR SEPTAL OR ASYMMETRIC)

3. SEARCH: STENOSIS NEAR (MUSCULAR OR SUB ADJ AORT$3 OR SUB-AORT$3 OR SUBAORT$3)

4. SEARCH: HOCM OR IHSS OR HCM

5. SEARCH: 1 OR 2 OR 3 OR 4

6. SEARCH Death-Sudden-Cardiac#.DE.

7. SEARCH 6 AND (hypertroph$2 or HYPERTROPHY-LEFT-VENTRICULAR#.DE.)

8. SEARCH 5 or 7

Above Search combined with publication type filters: RCT, SR, cohort filter as below:

Medline RCT filter:

1. SEARCH: PT=RANDOMIZED-CONTROLLED-TRIAL

2. SEARCH: PT=CONTROLLED-CLINICAL-TRIAL

3. SEARCH: (SINGL$4 OR DOUBLE$4 OR TRIPLE$4 OR TREBLE$4) AND (BLIND$4 OR MASK$4)

4. SEARCH: RANDOM$5 OR PLACEBO$2

5. SEARCH: RANDOM-ALLOCATION.DE.

6. SEARCH: DOUBLE-BLIND-METHOD.DE.

7. SEARCH: SINGLE-BLIND-METHOD.DE.

8. SEARCH: (CLINIC$3 NEAR TRIAL$2).TI,AB.

9. SEARCH: RETRACT$5 NEAR PUBLICATION

10. SEARCH: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9

11. SEARCH: ANIMAL=YES NOT HUMAN=YES

Medline SR: filter: [NOTE if this were re-run again there will be some changes in the indexing]

1. SEARCH: REVIEW-LITERATURE#.DE.

2. SEARCH: PT=META-ANALYSIS

3. SEARCH: META-ANALYS$

4. SEARCH: (META ADJ ANALYSIS).TI,AB.

5. SEARCH: META-ANALYSIS#.DE.

6. SEARCH: METAANALYSIS

7. SEARCH: (SYSTEMATIC NEAR (REVIEW$3 OR OVERVIEW)).TI,AB.

8. SEARCH: (QUANTITATIV$2 NEAR (REVIEW$3 OR OVERVIEW$2 OR SYNTHESIS$2)).TI,AB.

9. SEARCH: (METHODOLOGIC$ NEAR (REVIEW$3 OR OVERVIEW)).TI,AB.

10. SEARCH: (INTEGRATIVE ADJ RESEARCH ADJ REVIEW$3 OR RESEARCH ADJ INTEGRATION).TW.

11. SEARCH: (REFERENCE ADJ LIST$ OR BIBLIOGRAPH$3 OR HAND-SEARCH$3 OR HAND ADJ SEARCH$3 OR RELEVANT ADJ JOURNALS OR MANUAL ADJ SEARCH).AB.

12. SEARCH: (REFERENCE ADJ LIST$2 OR BIBLIOGRAPH$3 OR HAND-SEARCH$3 OR HAND ADJ SEARCH$3 OR RELEVANT ADJ JOURNALS OR MANUAL ADJ SEARCH).AB.

13. SEARCH: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12

14. SEARCH: (MEDLINE OR MEDLARS OR PUBMED).AB.

15. SEARCH: (SCISEARCH OR SCIENCE ADJ CITATION ADJ INDEX OR BIDS).AB.

16. SEARCH: (PSYCHINFO OR PSYCINFO OR PSYCHLIT OR PSYCLIT).AB.

17. SEARCH: (COCHRANE OR EMBASE OR CINAHL OR CINHAL).AB.

18. SEARCH: DATABASE$2 AND (ELECRONIC OR BIBLIOGRAPHIC OR COMPUTERISED OR COMPUTERIZED OR ONLINE OR ON ADJ LINE).AB.

19. SEARCH: SELECTION ADJ CRITERIA OR DATA ADJ EXTRACTION

20. SEARCH: 14 OR 15 OR 16 OR 17 OR 18 OR 19

21. SEARCH: 20 OR 13

22. SEARCH: PT=COMMENT OR PT=LETTER OR PT=NEWSPAPER-ARTICLE

23. SEARCH: 21 NOT 22

Medline Cohort Filter:

1. Cohort-Studies#.DE

2. cohort$2.TI,AB

3. (prospectiv$2 OR retrospectiv$2).TI,AB

4. 1 OR 2 OR 3

Embase on Dialog Datastar 1996 (EMED)-date [05/02/08]

Limits: Years 2003-current, English language

1. SEARCH: HYPERTROPHIC-CARDIOMYOPATHY#.DE..

2. SEARCH: HYPERTROPH$4 NEAR (CARDIOMYOPATH$4 OR STENOSIS OR SEPTAL OR ASYMMETRIC)

3. SEARCH: STENOSIS NEAR (MUSCULAR OR SUB ADJ AORT$3 OR SUB-AORT$3 OR SUBAORT$3)

4. SEARCH: HOCM OR IHSS OR HCM

5. SEARCH: 1 OR 2 OR 3 OR 4

6. SEARCH Death-Sudden-Cardiac#.DE.

7. SEARCH 6 AND ((hypertroph$4) or (Heart-Left-Ventricle-Muscle.DE..))

8. SEARCH 5 or 7

Embase RCT filter:

1. SEARCH: (RANDOM$ OR PLACEBO$).TI,AB.

2. SEARCH: (SINGL$4 OR DOUBLE$4 OR TRIPLE$4 OR TREBLE$4).TI,AB. AND (BLIND$4 OR MASK$4).TI,AB.

3. SEARCH: (CONTROLLED ADJ CLINICAL ADJ TRIAL).TI,AB.

4. SEARCH: RANDOMIZED-CONTROLLED-TRIAL#.DE.

5. SEARCH: 1 OR 2 OR 3 OR 4

Embase SR filter

1. SEARCH: REVIEW-LITERATURE#.DE.

2. SEARCH: PT=META-ANALYSIS

3. SEARCH: META-ANALYS$

4. SEARCH: (META ADJ ANALYSIS).TI,AB.

5. SEARCH: META-ANALYSIS#.DE.

6. SEARCH: METAANALYSIS

7. SEARCH: (SYSTEMATIC NEAR (REVIEW$3 OR OVERVIEW)).TI,AB.

8. SEARCH: (QUANTITATIV$2 NEAR (REVIEW$3 OR OVERVIEW$2 OR SYNTHESIS$2)).TI,AB.

9. SEARCH: (METHODOLOGIC$ NEAR (REVIEW$3 OR OVERVIEW)).TI,AB.

10. SEARCH: (INTEGRATIVE ADJ RESEARCH ADJ REVIEW$3 OR RESEARCH ADJ INTEGRATION).TW.

11. SEARCH: (REFERENCE ADJ LIST$ OR BIBLIOGRAPH$3 OR HAND-SEARCH$3 OR HAND ADJ SEARCH$3 OR RELEVANT ADJ JOURNALS OR MANUAL ADJ SEARCH).AB.

12. SEARCH: (REFERENCE ADJ LIST$2 OR BIBLIOGRAPH$3 OR HAND-SEARCH$3 OR HAND ADJ SEARCH$3 OR RELEVANT ADJ JOURNALS OR MANUAL ADJ SEARCH).AB.

13. SEARCH: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12

14. SEARCH: (MEDLINE OR MEDLARS OR PUBMED).AB.

15. SEARCH: (SCISEARCH OR SCIENCE ADJ CITATION ADJ INDEX OR BIDS).AB.

16. SEARCH: (PSYCHINFO OR PSYCINFO OR PSYCHLIT OR PSYCLIT).AB.

17. SEARCH: (COCHRANE OR EMBASE OR CINAHL OR CINHAL).AB.

18. SEARCH: DATABASE$2 AND (ELECRONIC OR BIBLIOGRAPHIC OR COMPUTERISED OR COMPUTERIZED OR ONLINE OR ON ADJ LINE).AB.

19. SEARCH: SELECTION ADJ CRITERIA OR DATA ADJ EXTRACTION

20. SEARCH: 14 OR 15 OR 16 OR 17 OR 18 OR 19

21. SEARCH: 20 OR 13

22. SEARCH: PT=COMMENT OR PT=LETTER OR PT=NEWSPAPER-ARTICLE

23. SEARCH: 21 NOT 22

Embase Cohort filter:

1. SEARCH: COHORT-ANALYSIS#.DE.

2. SEARCH: MASS-SCREENING#.DE.

3. SEARCH: LONGITUDINAL-STUDY#.DE.

4. SEARCH: PROSPECTIVE-STUDY.DE.

5. SEARCH: FOLLOW-UP#.DE.

6. SEARCH: (COHORT$2 OR LONGITUD$5).TI,AB.

7. SEARCH: 1 OR 2 OR 3 OR 4 OR 5 OR 6

Appendix B

Table 6 Summary of studies estimating the prevalence of HCM

Author, location, year, reference	Time period	Cases	Prevalence	Male : female ratio	Age group	Design	Population	Diagnosis	Comments
Maron *et al*, (Minnesota, USA)[69]	1987-1988	7	0.17% (7/4111) 170/100,000 0.26% - Men 0.09% - Women 0.24% - White 0.1% - Blacks	2.9:1	23-35 years of age	Population based observational study	General population in four urban centre randomly selected and stratified (N=4111)	2D-echocardiography hypertrophic (≥ 15 mm), non-dilated LV, in absence of HT (probable or definite HCM)	Study excluded those who could not undertake an exercise test because of cardia or systemic symptoms, but numbers not provided. This might have included some mildly symptomatic people with HCM Those initial screen were assessed in more detail Blind assessment of echocardiograph
Codd *et al*, (Minnesota, USA)[185]	1975-1984	19	0.0197% 19.7/100,000 (age and sex adjusted)	NR	16-94 years	Population based			Prevalence at 1985
Savage *et al*, (USA)[186]	1983	NR	0.0197% (~19.7/100,000)	NR			Framingham study		
Maron *et al*, (Arizona, Oklahoma & Dakota, USA) [187]	1993-1995	NR	0.23% (8/3501)	NR	51-77 years	Population based observational study N=3501	American Indian community from reservations hospitals	2D-echocardiography hypertrophic (≥ 15 mm), non-dilated LV, in absence of HT (probable or definite	91.1% of cohort not have echocardiography and not included in study Blind assessment of echocardiographs by 2

								HCM)	independent investigators
Bjarnason *et al*, 1982, (Iceland)[188]	1966-1977	11	0.033% 33/100,000	NR			Extrapolation from cases identified at autopsy		
Miura *et al*, (Japan)[56]	1999	7262	0.173% 17.3/100,000 (crude)	2.3		Cross sectional study of hospitals, stratified and randomly selected	96.2% were diagnosed with echocardiographic. WHO/ISFC 1980 definition used[189]	Hospitals units asked to identify number of cases	Medium response rate (58.4%) but this varied considerably by department (44.9%-95.8%) Prevalence increased with age for men and women under <70 years and thereafter. 78% of cases of were >50 years (12.3% were <40 years)
Ino, 1996, (Japan)[156]	1981-1992	10	0.02% 20/100,000	NR	7-8 years and 12-13 year	Population based, Adachi ward, Tokyo	Children	2D echocardiography	
Hada, 1987 (Japan)[190]		NR	0.17%	NR	20-77 years		Working population		Under-estimate of the birth prevalence of those at risk of developing HCM
Arola *et al*, (Finland)[57]	1980-1991	40	2.9/100,000 (CI 95%, 2.0-4.0)	3:1	<20 years	Retrospective population-based study	All patient identified from all tertiary centre and death certificates, but very close to a population based study	WHO criteria. Echocardiography, echocardiography, and catheterisation and catheterisation and angiocardiography, autopsy hypertrophic (≥ 2 s.d. of normal values according to age and body surface area), non-dilated LV, in absence of HT (probable or definite HCM)	Data from 1987 onward only could be used (ICD 9) No significant change in incidence between 1980-85 and 1986-91

Zou *et al*, (China)[191]	2001-2002	13	0.16% 0.08% (age and sex adjusted) 80/100,000	2.25	Random stratified sample from nine communities in nine provinces (N=8080)	Non dilated ventricular hypertrophy by echocardiography	2D-echocardiography hypertrophic (≥ 13 mm), non-dilated LV, in absence of HT (probable or definite HCM)	Same family enrolment excluded. Non previous HCM reported. Male have higher prevalence until >60 years , when women predominate 46% case <39 years

Table 7. Summary of studies estimating the incidence of HCM

Author, location, year, reference	Time period	Cases	Incidence rate	Male: female ratio	Age group	Design	Population	Diagnosis	Comments
Codd *et al* (Minnesota, USA)[185]	1975-1984	19	2.5/100,000 (age and sex adjusted)	2:1	16-94 years	Population based			Incidence doubled to 3.6/100,000 from first to last 5 years of study
El-Menyar *et al*,(Qatar) [53]	1996-2003	18	3.1/100,000 incidence 2.6/100,000 (children)	NR	< 50 years	Population based	Main tertiary hospital used for all cardiomyopathies, excluding CHF complicating acute MI and end-stage rheumatic valvular heart disease	Echocardiography septal wall thickness (≥ 15 mm), dilate atrium (>cm) and LV end diastolic diameter <45mm	Increasing incidence was between 1992 and 1995 was put down to increases awareness of HCM 15% of cases < 15 years.
Bagger *et al*, 1984 (West Denmark)[192]	1980-1981	20	0.4/100,000	NR	NR	Population based	Cases from three referral centres and pathology department		
Nugent *et al*, (Australia)[54]	1987-1996	80	0.3/100,000 (CI 95%0.25-0.398)	2:2	<10 years at presentation	Retrospective population-based study	All children referred to Australian paediatric tertiary services	WHO classification Echocardiography Unexplained septal hypertrophy, LV free-wall thickness > s.d. above normal mean) or RV free-wall thickness >4mm	Rates fall with age by a factor of 19, from 1.89 in <1 year olds to 0.1 in 5-10 year olds. No evidence of change over time and little regional variation
Maron *et al*, (Baltimore, USA)[193]	1981-1987	26	0.046% 4.6/100,000 live births	NR	NR	Controlled prospective study	Infants		N=5460
Arola *et al*, (Finland)[57]	1980-1991	40 (+ 4 with earlier	0.24/100,000 (CI 95%, 0.17-0.33)	3:1	<20 years	Retrospective population-based	All patient identified from all tertiary centre and death certificates	WHO criteria. Echocardiography, echocardiography, and catheterisation and	Data from 1987 onward only could be used (ICD 9) No significant change in

		diagnosis)				study	catheterisation and angiocardiography, autopsy hypertrophic (≥ 2 s.d. of normal values according to age and body surface area), non-dilated LV, in absence of HT (probable or definite HCM)	incidence between 1980-85 and 1986-91 Disease occurrence tended to increase slightly with age 39% 99(26/44) of patients > 15 years at presentation. 61% (27) were asymptomatic at presentation, systolic murmur being the prime reason for examination. Only 20% (9) had abnormal ECG/radiograph
Miura *et al* (Japan)[56]	1999	7262	4.14/100,000	NR	NR	Cross sectional study of hospitals, stratified and randomly selected	Used WHO/ISFC 1980 definition[189] Hospitals units asked to identify number of cases, with 96.2% using echocardiographic for diagnosis,	Medium response rate (58.4%) but this varied considerably by department (44.9%-95.8%) Incidence calculation was based on a second survey.

Appendix C

Table 8. Summary of non-UK studies reporting sudden cardiac deaths due to HCM as a proportion of all sudden cardiac deaths

Author, location	Time period	Age – group	HCM (%)	HCM cases	SD (classifiable)	% HCM of SCD	SCD	Population	Type of study	Comment
Drory *et al*, Israel[194]	1976-1985	9-29	>8%*	13*	162	>11%*	118		Retrospective review	*No figure provided for >30 age group. If assumed that no HCM was found in this aged group then it would be> 8% at minimum (13/162 cases). HCM was 22% of SCD <20 years and 13% of SCD 20-29 years
Eckart *et al*, USA[195]	1977-2001	18-35	6.3%	8	126	12.5%	64	6.3 million (Military recruits (males and female)	Retrospective autopsy review	Of 277 deaths, 126 non-traumatic deaths had reports. 64 had an identifiable cardiac abnormality (two-thirds in males aged 17-19 (44). 45% due to coronary artery disease, plus 16% due to atherosclerosis, 36% cardiomyopathy (of which 12.5% (8) were due to HCM), and 3% misc. cardiac deaths. However, only one of the 8 HCM showed myocyte disarray. 6.3% of all non-traumatic sudden deaths were due to HCM. 6.3% of SD were due to HCM
Wisten *et al*, Sweden[196]	1992-1999	15-35	NR	19	NR	10.5%	181	Swedish population	Retrospective autopsy review	181 SCD identified, 162 excluding aortic aneurysms. Those 66 with ECG compared to autopsy. All 11 HCM cases were men, 9 with pathological ECG. 73% of SCD were male. More males than females for all ages over 17. 52% (10/19) HCM SCDs were <30 year olds
Tiziana di Gioia, Italy[197]	2001-2005	1-40	2.8%	4	141	4%	100	Lazio (5,264,077)	Prospective autopsy review	Excluded SIDS. HCM morphologically, toxicologically and histologically defined. 30% due to coronary artery disease, 24% due to atherosclerosis
Corrado *et al*, Italy,[71]	1979-1999	12-35	7.6%	23	300	8.8%	259	Veneto	Retrospective autopsy review	All sudden unexpected deaths are required by law to be investigated as in the UK

		(1,386,600)	300 sudden deaths of 41 were non-cardiovascular or unexplained

Appendix D

Table 9.RCTs of treatment of HCM: outcomes measures, assessment and follow-up

Author & Year (Country)	Population (NYHA Class)	Mean age (s.d. /range)	N	Duration of study	Outcomes	Results			Comments
						Comparator 1	Comparator 2	Comparator 3	
B-blockers									
Cohen, 1968 (USA) [115]	Class II (implied)	34(±7.8)	8			Propranolol	Placebo		
					1. Exercise duration – treadmill testing			5/8 improved their exercise duration significantly	Incomplete data
Hubner, 1973 (UK)[118]	Class I: 2 Class II: 9 Class III: 5	36 (21-58)	16	3 months	1. Symptoms – diary card + scoring method	Propranolol	Practolol	Placebo	Symptoms recorded 21 days in middle of 28 day treatment period. Higher score – more symptoms No clear if correct analysis was used. Did not look at long term outcomes
						n=16	n=16	n=16	
					1a.Dyspnoea	8.1	6.6	3.0	There was no statistical difference between treatment for Class I & II patients but was for Class III
					1b. Angina	2	1	5	p=0.06 for propranolol p=NS for practolol
					1c. Syncope	0/0	1/0	1/0	p=NS (drugs vs. placebo)
					1d. Palpitations	4/6	6/11	8/14	p=NS for both drugs.
					1e.Dizziness no. of patients experiencing	46	8/9	6/10	p=NS

					symptom]					
					1f. Headache	6/8	8/9	10/14		p<0.01 for propranolol only
					1g. GIT upset	4/4	1/1	2/2		p=NS
					1h.Wheezing	2/2	2/2	2/2		p=NS
					2. LV ejection time – apexcardiogram + phonocardiography (ms)	454.3(±9.5)	428.4 (±10.2)	431.5 (±9.0)		LVET, p=0.006 for propranolol
Swanton *et al*, 1977(UK)[128]	Class I: 1	33.0 (±12.5)	8	30 mins after drug ingestion		Propranolol	Practolol			Pre-treatment with diazepam + atropine to see impact on paced heart rate+ No long—tem follow up Mean difference
	Class II: 1					n=4	n=4			
	Class III: 6				1. LV end-diastolic volume index (LVEDVI)	NR	NR			Data in figures. Both groups p<0.01
					2. LV end-systolic volume index (LVESVI)	NR	NR			Data in figures. Both groups p<0.002
					3. Stroke volume index (SVI)	NR	NR			Data in figures. Both groups p=NS
					4. Normalise ejection rate	NR	NR			Data in figures. Both groups p<0.01
					5. Peak LV Pressure (Hg mm)	-8 l (combined)	- 8 (combined)			Drugs analysed together causes no change in mean pressure p=NS
					6. LV end diastolic pressure (LVEDP)(Hg mm)	-5.1 (combined)	-5.1 (combined)			Drugs analysed together causes a mean fall in LVEDP, p=NS
Storstein *et al*, 1981(Norway)[126]	Class I: 1	38.2 (±17.2)	10	4 days		Propranolol	Strophanthin	Practolol	Placebo	
						n=10	n=10	n=10	n=10	
	Class II: 8 Class III: 1				1. Exercise work load (k.p.m.)	7470 ± 2783	6960± 2203	7560± 2552	6790± 2758	p=NS Heart rate also dropped significantly for practolol and propranolol only

Rosing *et al*, 1982, (USA) citied in Rosing *et al* [198]	Non specified but says same as later study which had non obstrucutive HCM patients	44(21-70)	27	Short-term (5 days)		Nifedipine	Verapamil	Placebo	Infusions given at three strengths
					1. Exercise duration – testing (mins)	6.6±2.8	7.7±3.3	5.5±3.3 (mins)	p<0.02 for nifedipine compared with placebo p<NS for verapamil compared with placebo
							38 +/- 58%	NR	In a separate study, verapamil improved exercise duration by compared with placebo (p = 0.02)
Pollick, 1988 (Canada)[116]	Class I: 4 (implied)	48 (32-68)	10	18 days		Propranolol	Disopyramide	Placebo	
	Class II: 6 (implied)					n=10	n=10	n=10	
					1. Exercise duration – treadmill testing (mins)	8.8 (±2)/9	10.4 (±2)/9	9.6 (±2)/9	Only 9 patients completed all three test. One patient was pre-syncopal on propranolol (did not do test) but OK on disopyramide.
					2. Unstable rhythm – 24hr Holter – (mean no. of ventricular premature complexes)	3/hr	0/hr	>10/hr	Disopyramide vs. placebo, p<0.01 Propranolol vs. placebo, p<0.01
					3. Sub-aortic pressure gradient – echo – (mmHg).	30/30	5/15	61/20	Disopyramide vs. placebo, p<0.01 Propranolol vs. placebo, p<0.01 Propranolol vs. Disopyramide, p<0.01
					4. LV ejection time - echocardiography - (ms)	322/41	314/26	352/52	Disopyramide vs. placebo, p<0.01 Propranolol vs. placebo, p<0.01
Gilligan, 1993	Class I: 8	39 (±17)	18	14 weeks		Nadolol	Verapamil	Placebo	

(UK)[113]										
	Class II: 10					n=16	n=16	n=16		10 patients became medication free before study Patients preferred drugs over placebo, p=0.001
					1. Symptoms	11.0 (±6.4)	9.0 (±6.4)	10.5 (±7.7)		p=NS for all comparisons
					2. Exercise duration – exercise ECG (secs)	476 (±85)	525 (±94)	530 (±104)		p=NS
					3. Max V02 consumption – (ml/Kg/min)	21 (±7)	23 (±6)	26 (±8)		p=NS
					4. Unstable rhythm – 24hr Holter – (No. of pts with sinus pauses > 1.5 secs (SP & no of pts with episodes of VT (VT))	11 SP, 3 VT	8 SP, 1 VT	6 SP, 4 VT		
Thaman *et al*, 2005 (UK)[100]	Class I: 13	31(±8)	21	21 weeks		Propranolol	Clonidine	Paroxetine	Placebo	All patients showed ABPR during a standard erect cycle test 3 patients had ICDs but no discharges Statistical analysis compares measurements at baseline with those at 3 weeks of medication
	Class II: 17									No change between baseline and placebo. Studies focuses on ABPR – failure to rise >25 mmHg or fall <10 mmHg but no data provided on this.
	Class III: 1				1. Exercise testing (mins)	7.6 (±1.9)	7.3 (±1.6)	7.6 (± 16)	7.8 ± (1.0)	p=NS for all drugs and placebo
					2. %VO2 max	70 (±17)	74 (±16)	72 (± 16)	76 (± 17)	p=NS for all drugs and placebo
					3. Heart rate rest (beats/min)	60 (±7)	69.0 (±13)	71 (± 11)	79 (± 11)	Propranolol, p=0.03. P=NS for all other drugs and placebo
					4. Heart rate peak (beats/min)	130 (±22)	148 (±18)	146 (±30)	148 (±20)	Propranolol, p=0.02. P=NS for all other drugs and placebo
					5. Systolics BP change	16 (± 6)	16.8 (±5.3)	26.5 (±7.5)	18 (±8)	Paroxetine, p=0.02. P=NS for all other drugs and placebo
					6. Forearm vascular resistance (FVR)	NR	NR	NR	NR	Only for Group A (fall in lower body negative pressure) vs. Group B (rise in lower body

					change					negative pressure). Figure shows paroxetine rises significantly statistically, but changes in other drugs and placebo are NS.
					7. Forearm blood flow (FBF) change	NR	NR	NR	NR	Only for Group A (fall in lower body negative pressure) vs. Group B (rise in lower body negative pressure)
										Significant change in Group A (but not B) for all drugs but not placebo
Tendera, 1993 (Poland)[114]	Class II: 22	36(±8)	30	10 days		Sotalol	Placebo			14 day washout for patients on Verapamil
	Class III: 8					n=30	n=30			21/30 patients improved their
					1. Exercise duration – bicycle stress test (mins)	10.6 (±4.0)	9.4 (±3.6)			Sotalol increase exercise time, p<0.01. Of the 25 who benefits, they were followed-up over 6 months, with improvement in exercise time (12.7 (±3.2), p<0.01)
					2. Unstable rhythm – 24hr Holter – SVT	1/30	7/30			Sotalol eliminated SVTs in 6 of the 7 people with them, p<0.003
					3. Unstable rhythm – 24hr Holo ter – Arrhythmias.	6/30	13/30			Sotalol suppressed VAs in 6 of the 13 people with them, p<0.05
					4. Unstable rhythm – 24hr Holter – VT.	4/30	8/30			Sotalol abolished VTs in 4 of the 8 people with them, but appeared in one sotalol patient who was free from them on placebo. No stats provided. Six of the 8 who saw improvement were followed over six months at an increased dose, with VT abolished in 4 patients but this was NS (p=0.2)
Ca^{2+} blockers										
Toshima, 1986 (Japan)[117]	Class I:7	42(±15)	32	4 weeks		Verapamil	Diltiazem			
	Class II:21					Group A (n=14)	Group A (n=14)	Drug effect (excluding		Diltiazem and Verapamil.

						Group B (n=18)	Group B (n=18)	sequence and period effects)	More side effects on Verapamil
	Class II: 4				1. Exercise stress test (mean diff in mins)	2.3 (Grp A) 2.0 (Grp B)	1.0 (Grp A) 1.8 (Grp B)	0.0 (±0.3)	p=NS between drugs
					2. Maximum V02 consumption on stress testing – (ml/Kg/min)	3.8 (Grp A) 2.9 (Grp B)	1.8 (Grp A) 3.3 (Grp B)	0.1 (±0.6)	p=NS between drugs
					3. LV ejection fraction – Echo – (diff in %)	0 (Grp A) 2 (Grp B)	-1(Grp A) -1(Grp B)	-0.6 (±1.0)	p=NS between drugs
Gistri, 1994 (Italy)[119]	Class I: 12	40(±10)	20	10 weeks		Verapamil	Placebo		Poor selection of patients. Patients with septal mean septal thickness = 24mm ±6 mm No medication one week before trial entry
	Class II: 8					n=9	n=9		Two drop outs due to side effects
					1. Exercise duration – bicycle stress test (diff mins)	0	1		p=NS
					2. LV outflow tract gradient – echo (mm/Hg)	-3	-10		P=NS
					3. Transmural blood flow – PET scanner (ml/min/g) (Theory: improved blood flow should prevent ischaemia and conduction problems in thickened septum)	[13]	See comments		Available for only 7/20 patients with large septums >25mm Remained unchanged. 2/7 were did not receive dipyridamole NS difference between groups on treatment and placebo on dipyridamole
Angiotensin-type II receptor agonists									
Kawano *et al* 2005 (Japan)[111]	Non obstructive HCM only	63.6	23	12 months		Valsartan + conventional RX	Conventional Rx		Patients were on β-blockers (12), Ca^{2+} agents (8) or both (2). NS difference between groups. No placebo.
						n=11	n=12		
					Brain natriuretic peptide (BNP)	NR	NR		p=NS, data in figures
					Troponin (TnT)	NR	NR		p=NS, data in figures

					Aldosterone (mean diff. pg/ml)	2.7	23.4	Valsartan group remained unchanged over time p=0.27, but Conventional Rx increased, p<0.05). No mean difference comparison but SE in figures indicate non significant results
					Pro-collagen type I (PIP)(mean diff. ng/ml)(Theory is the PIP acts as marker for cardiac fibrosis)	-20.4	9.9	Conventional Rx remained unchanged over time p=0.22, but valsartan decreased, p<0.05). No mean difference comparison but SE in figures indicate non significant results
					LV wall thickness (mean diff. mm)	-0.2	-0.4	p=NS
					LV Ejection Fraction (LVEF) (mean diff %)	-0.3	-0.7	p=NS
Yamazaki *et al*, 2007 (Japan)[125]	Non obstructive HCM only	56.8 (±)	19	12 months		Losartan Ka^{2+*} Conventional Rx	Conventional Rx	ARBs are contraindicated in HOCM Population had normal LVOTG No placebo. Anti-hypertensive drugs taken to control BP if necessary (ARB Grp:1, non ARB Grp: 3). P=NS between groups
	(i.e. mainly Class I)					n=9	n=10	All male
					LV Mass (LVM) (Theory ACE inhibitors ameliorate the process of myocardial hypertrophy) (mean diff. cm^3)	-18	2	Intragroup p=0.07 over year for Losartan p=NS over year for no Losartan Intergroup p=NS for $LVM_{Initial}$ or LVM_{Final}
					Normalised LVM (=$LVM_{Initial}/LVM_{Final}$)	0.93 (±0.10)	1.02 (±0.07)	p=0.03 for Normalised LVM
Lipid lowering drugs								
Bauersachs *et al*, 2007(Germany)[122]	NR but mean septal thickness was 16.5 (±3.5) mm and LVEF was 66.6%	48.1 (±)	28	9 months	(Theory statins block myocyte stress signals which result in increased hypertrophy) (mean diff. g)	Atorvastatin	Placebo	6 people dropped out the study, 3 in each arm, one due to increase in liver enzymes

	suggesting inclusion of asymptomatics					n=14	n=14		12 patients on B-blockers and 9 on Ca^{2+} agonists. P=NS between groups
					% change in LV Mass (LVM)	2 ± 10	0 ± 13		Intragroup p=NS for placebo over 9 months p=NS for Atorvastatin over 9 months Intergroup p=NS
					% change End diastolic volume, (ml)	–1 ± 21	5 ± 21		
					% change End systolic volume (ml)	3 ± 27	5 ± 32		
					% LVEF (echo)	0 ± 10	1 ± 10		
					% LVEF (CMR)	–1 ± 9	1 ± 11		
DDD									
Nishimura, 1997 (USA)[112]	Class II: 2 Class III:16 Class IV: 2	58 (35-74)	21	6 months		DDD pacing mode -first	AAI back up mode-first	Baseline	HOCM, refractory to treatment., 12 with exertional angina
						(n=8/19)	(n-11/19)		
					1. Symptoms – New York Heart Association Class (NYHA) (higher no – more symptoms)	2.4 ± 0.7	2.6 ± 0.7	2.9 ± 0.4	Mean (±s.d.) 63% patients had symptomatic improvement in DDD (5% a deterioration) but only 42% with AAI
					2. Wellbeing – Quality of life score (lower no = better wellbeing)	41.6 ± 25.9	48.4 ± 23.2	55.1 ± 23.7	p<0.05 between baseline and DDD NS difference between DDD and AAI
					3. Exercise duration – treadmill (minutes)	6.9 ± 2.2	6.3 ± 2.3	5.7 ± 2.7	Exercise tolerance increased in DDD from baseline (p<0.05), p=NS difference between DDD and AAI
					4. LV output gradient – echo (lower mm Hg	54.9 ± 38.0	83.4 ± 59.0	76.7 + 61.0	p<0.05 for DDD vs. baseline and AAI

					= better)				
					5. Max V02 consumption – ml/Kg/min (higher no = better)	20.0 ± 6.5	19.8 ± 6.1	19.4 ± 6.7	p=NS from baseline and between arms.
Kappenberger, 1997, (Switzerland)[120]	Class II/Class III Mean, 2.55 (±0.5)	52.9 (±14.9)	83	6 months		DDD	DDD turned-off		Twelve participating European centres in M-PATHY study 42 patients on B-blockers, 39 on Ca^{2+} agonists, 12 on amiodarone, 3 on disopyramide, 10 diuretics and 3 ACE inhibitors A cohort was subsequently followed for 36 months (5 patients)
						n=40	n=42		I died and 2 people dropped out, one from each arm
					1. Exercise testing (mins)	8 (Grp A& B)	NR		No stats provided
					2. LVOT (mean diff. mmHg)	-25±20 (Grp A) -45±28 (Grp B)	-20 (Grp A) Non (Grp B)		No stats provided
					3. Symptoms – NYHA				No stats provided Four chose to turn DDDs off, 76 remained on , 54% of which were reclassified as Class I
					4. Wellbeing – Quality of life score (lower no = better wellbeing)				No stats provided At 36 months 75% of patients remain happy with treatment
Gadler *et al*, 1999 (Sweden)[123]	Class II: 3 Class III: 7	64.1±9.8	10	24 weeks		DDD	AAI mode (inactive mode)	Baseline	All patients had received DDD ≥ 6 months Four on β-blockers and 4 were on Ca^{2+} agonists.
	After entry into trial					n=10	n=10	n=10	
	Class I: 7 Class II:3				1. Exercise testing (mins)	Data in figure	Data in figure	Data in figure	No stats provided
					2. Wellbeing – Quality of life score (lower no = better wellbeing)	0.89 1.53 0.32 0.27	2.44 2.26 0.78 0.49	Chest pain Dyspnea Palpitations Dizziness	p<0.01 NS p<0.06 NS

Mickelsen *et al*, 2004 (USA)[124]	HOCM	47 ± 22	11	3 months		DDD opt	AVI-30(DDD-30)	AAI back up	Optimizing the AVI was associated with improved exercise tolerance p< 0.05) and improved QOL.
						n=11	n=11	n=11	
					Exercise testing – treadmill (min)	4.6±2.3	5.5 ± 2.2	7.7 ± 2.5	Stats provided in figure shows Exercise testing using Bruce protocol with 95% CIs overlapping implying p=NS for all
					Wellbeing – Quality of life score (lower no = better wellbeing)	62 ± 16	42± 12	Physical function	p< 0.05
						73 ± 14	53 ± 11	Role physical	p< 0.05
						67 ± 17:	50 ± 13	General health	p< 0.05
						66 ± 16	46 ± 12	Vitality	p< 0.05
									p=NS for bodily pain, social function, role, emotional, and mental health
Maron, 1999 (USA)[121]	Class II: 11 Class II/IV: 37	53±17	48	6 months		DDD pacing	AAI back up	Baseline	Multicentre trial, followed by unblinded 6 months trial
									4 people dropped out.
									Medication: β-blockers (65%), Ca^{2+} agonists (principally verapamil) (46%), disopyramide (23%), and diuretic agents, (27%), alone or in combination.
									55% experienced adverse events, 8 device malfunction and 14 other including 1 SCD. Annual mortality 2.3%
					1. LVOG (mmHg)	48±33	76±32	82±33	Intra-arm
									p=<0.001between DDD and baseline
									Inter-arm
									p=<0.001between DDD and AAI
					2. Peak V02 (ml/min/kg)	16.7±4	16.6±5	16.2±5	Intra-arm
									p=NS between DDD and AAI
									p=NS for DDD (at 12 months)
					3. Exercise testing – treadmill (min)	10.7±4	10.6±3	9.2±4	Intra-arm
									p=NS between DDD and AAI
									No stats provided for baseline and DDD or AAI

4. Wellbeing – Quality of life score (lower no = better wellbeing)	34±24	36±23	48±22	Intra-arm p=NS between DDD and AAI No stats provided for baseline and DDD or AAI p<0.0001 for DDD (at 12 months)
5. Wall thickness - anterior (mm)	21±4	23±4	22±5	Inter-arm p=NS between DDD and AAI and baseline

Table 10. RCT of treatment of HCM: Outcome measures, assessment and follow-up

Author & Year (Country)	Design	Power calculation	Allocation concealment	No differences between groups	Double/ Single blind (db/sb)	Sufficient wash out period	No attrition	Intention to treat analysis	Any differences adjusted for in analysis	Statistical test/analysis OK
β-blockers										
Cohen, 1968 (USA) [115]	RXT	No	No	NA	Yes (sb)	No - 1 day	Yes	NR	NA	NR
Hubner, 1973 (UK)[118]	RXT	No	No	NA	Yes (db)	Yes - 3 - 4 days	No -2 withdrawals	No	NA	NR
Swanton *et al*, 1977(UK)[128]	RCT	No	No	NR	No	NA	Yes	Yes	NR	NR
Storstein *et al*, 1981(Norway)[126]	RXT	No	No	NA	Yes (db)	No	No	Yes	NA	Yes
Rosing *et al*, 1985, (USA)[198]	RCT?				Yes (db)					
Pollick, 1988 (Canada)[116]	RXT	No	No	NR	Yes (db)	No - 2 days	Yes	Partial (not clear for exercise testing)	NA	NR
Gilligan, 1993 (UK)[113]	RXT	No	No	NA	Yes (db)	Yes (1 week)	2 (for Nadolol use)	Yes	NA	Yes
Thaman *et al*, 2005 (UK)[100]	XT(cross-over trial)	No	Yes	NA	Yes (db)	Yes (3 weeks), No carry-over effects seen	Yes	Partial (not for Clonidine)	NA	Yes (paired t-test) ANCOVA)
Tendera, 1993 (Poland)[114]	RXT	No	No	NR	Yes (db)	No – direct switch of drugs	Yes	NA	NA	Partial (paired t-test)
Ca^{2+} blockers										

Toshima, 1986 (Japan)[117]	RXT	No	No	Yes	Yes (db)	Yes – I week	Yes	Yes	Yes	Yes (paired and unpaired t-test)
Gistri, 1994 (Italy)[119]	RCT	No	No	NR	Yes (db)	NA	No -2 patient in each group	Yes	No	Yes (paired t-test)
Angiotensin-type II receptor agonists										
Kawano *et al* 2005 (Japan)[111]	RCT	No	No	No	Partial (sb) only for biochemical assay	NA	No	Yes	NA	Yes (paired t-test) but not provided statistical for mean difference
Yamazaki *et al*, 2007 (Japan)[125]	RCT	No	Yes	No	Yes (sb)	NA	No	Yes	NA	Yes (paired and unpaired t-test)
Lipid lowering drugs										
Bauersachs *et al*, 2007(Germany)[122]	RCT	Yes	NR	N	Yes (db)	NA	No	No - not clear if analysis included those who dropped out	NA	Yes (including ANOVA)
DDD										
Nishimura, 1997 (USA)[112]	RXT	No	No	Yes	Yes (db)	No – assessed post-hoc	No – 2 dropped out	No -not clear if analysis included those who dropped out	NA	No (did not assess if period/carry over effect was at play as no wash out period)
Kappenberger, 1997,	RXT	No	No	Yes	Yes (db)	No – straight	No – 3 lost	NA	NA	Partial (used paired and

(Switzerland)[120]						switch	to follow-up			unpaired t-test but insufficient results provided)
Gadler *et al*, 1999 (Sweden)[123]	RXT	No	Yes	NA	Yes (db)	No – straight switch	No – 1 dropped out	NA	NA	Partial (used paired t-test but insufficient results /tests provided)
Mickelsen *et al*, 2004 (USA)[124]	RXT	No	No	NA	Yes (sb)	No – straight switch	No – 1 dropped out	NA	NA	Partial (used paired t-test but insufficient results /tests provided)
Maron, 1999 (USA)[121]	RXT	Yes	Yes	Yes	Yes (db)	No – straight switch	No – 4 in 6 months trial	NA	NA	No (did not assess if period/carry over effect was at play as no wash out period)

Appendix E

Table 11. Summary of the observational evidence on the effectiveness of ICDs in primary prevention of sudden cardiac death in asymptomatic or mildly limiting systematic HCM patients

Author, country, year	Intervention	Pop[n]	No. of asymptomatic or mild limiting symptoms (NYHA Class I & Class II)	Mean age (years) at implantation (s.d. /range)	Number of HCM study population (%)	Mean length of follow-up in months - primary prevention (range/s.d.)	Proportion of ICDs for primary prevention	Average length of follow-up primary prevention cohort (months)	Primary prevention appropriate discharge rate	Primary prevention annual discharge rate (95%CI)	Cumulative probability of appropriate discharge at 5 years (primary prevention)	Mean time to first appropriate discharge (years)	Comment
Jayatilleke *et al*, 2004 (Australia) [132]	ICD (own control)	Primary: 18, Secondary:4	NR	NR	22	34.8 (6-78)	81%	19 (1-52)	10%		NR	1.6 (0.08-4.5)	No difference in proportion in discharges in patients on medication (B-blockers/sotalol). VT triggered 6/7events. Used chi-squared but not results reported. Of those who had an appropriate primary discharge there wa a subsequent discharge rate of 10 % annually
Maron *et al*, 2007 (USA, Italy, Spain, Israel, Germany, Australia) [135]	ICD	Primary: 383 Secondary: 123	200 (52%) 127 (33%)	42 (±17)	506	44.4 (±33.6)	76%	NR	13%	3.6% (2.7-4.8)	17% (±2%)	16 patients between 5-10 years. Cumulative probability beyond 5 years was 27% (±7%)	130 of these participants had been previously followed in Maron *et al*'s study (2000). Only 35% of primary prevention candidates were known to have 1-4 RFs. Multivariate analysis did not show any specific risk factor linked with appropriate discharge (p=0.35), although most discharges in patients with one RF). Most participants were also on medication - different drugs did not seem to differ in the rate of inappropriate shocks (no stats provided).
Maron *et al*, 2000 (USA, Italy) [134]	ICD/ DDD(74%)	Primary: 85 Secondary:43	83 (65%): 27 (21%)	40 (±16)	128	37.2	66%	31.2	12% (10/85)	5%		NR	At time of implantation 26 of 29 with appropriate discharge were asymptomatic or had mild functional limitation (NYHA Class I and II) Most patient with appropriate discharges were <31 and > 55 years old
Marín *et al*, 2006	ICD	Primary: 27 Secondary:	NR	42.8 (±20.3)	45/726)	32 (median)	60%	NR	NR	1.6%	NR	NR	

(Spain)[65]		18, NYHA Class 1)			(6.2%)							(0.08-4.7)	
Begley *et al*, 2003 (USA)[133]	ICD/ DDD (40%)	Primary: 85 Secondary: 47	NR	34 (±17)	132	40.8 (± 38.4)	64%	40.8 (± 38.4)	NR	NR	16% (84% (±6%) - intervention free)	NR	33% of patients ≤ 20 years. Discharge rate was significantly lower in primary than secondary prevention by 20% points (64% ±7% vs. 84%±6%). Many patient (18%) had DDD, 22% myotomy and myomectomy) plus a few other interventions. 2 deaths were non cardiac RF: Appropriate shock was associated with age but not with any other risk factors
Przybylski *et al*, 2005 (Poland)[136]	ICD/ DDD (33%)	Primary: 28, Secondary: 18	NR	32 (±15.6)	46	28.2 (± 26.1) (whole group)	61%	28.2 (± 26.1) (whole group)	0.10	NR	NR	NR	No significant differences between primary and secondary in terms of length of follow-up
Woo *et al*, 2007 (Canada)[140]	ICD/ DDD (72%)	Primary: 50 Secondary: 11	NR	48 (18)	61	40 (±27)	82%	40 (±27) (whole group)	8% (4/50) (differed to secondary, p=0.08)	NR	~48% (whole group (P and S) -extracted from a graph)	2 (±1.1) (range 0.3-3.7) (whole group)	
Cha *et al*, 2007 (USA)[141]	ICD	Primary		43 (±16)	68	40.8 ± 26.4 (whole group)	100%	3.4 (±2.2)	13% (9/68)		16% (5-26)	1.9 (3 days-5.9 years)(whole group)	25% of cases underwent surgical septal myectomy before device placement. The average time to the first shock after implantation was 1.9 years (range, 3 days to 5.9 years) Studies appropriate discharges for VT but not VT or AF RF: hazard ratio for history of syncope or near syncope: 8.7 (95% CI 1.8–41.7)
Kaski *et al*, 2007 (UK)[137]	ICD/ DDD	Children (≤16 years) Primary: 17 Secondary: 5	11 (50%): 8 (36.4%)	14 (7-16)	22/160 (13.7%)	20.4 (12-27.6), primary prevention 1.4 years	77%	3.3 (median) (1.4-10)	5.9% (1/17) 4.1% (annual)	13% (all)	6.7% (93.7% 5-year shock free probability (95% CI 80-106%) i.e. NS)	0.13 (0.12-0.8)	≥2 RFs or previous cardiac event. 73% received dual chamber devices with ICD

Table 12. Critical appraisal of the observational evidence on the effectiveness of ICDs in the primary prevention of sudden cardiac death in people with HCM who are asymptomatic or have mildly limiting symptoms

Author, country, year	Potential confounders reported	Adjusted for confounders in analysis	Blinded case assessment	All participants accounted for	Accounted for in the analysis	Power calculation	Analysis appropriate	External validity	Complication rates	Other issues
Jayatilleke *et al*, 2004 (Australia) [132]	No	No	No	Yes	NR	No	No	3 tertiary centres	Inappropriate shock (primary): 9.1% (similar to secondary): infections, 4.5%:	Reimplantation due to post-operative bacterial endocarditis
Maron *et al*, 2007(USA, Italy, Spain, Israel, Germany, Australia) [135]	Yes	Yes	NR	Yes	NR	No	Yes	42 tertiary centres	Inappropriate shock (primary): 25% (similar to secondary): infections, 3.8%: Device related faults, 6.7%	
et al, 2000 (USA, Italy)[134]	No	No	Yes	Yes	NR	No	Yes	19 tertiary centres	Inappropriate shocks: 25% (primary and secondary): infections, 1.6%: Device related faults, 7.0%	Some patients ICD did not have capacity to store electrographic data. No numbers provided
Marín *et al*, 2006 (Spain)[65]	No	No	NR	Yes	NR	No	Partially	1 tertiary centre	Inappropriate shock (primary and secondary): 26.6%: infections, 2.2%; embolism, 4.5%	
Begley *et al*, 2003 (USA) [133]	Yes	No	NR	NR	NR	No	Partially (not multivariate, di not show differences between primary and secondary)	1 tertiary centre	Overall complications 29%. Inappropriate shocks in 23% (primary and secondary): %: infections, %; embolism, 4.5%; 5 cases of depression/anxiety	Follow-up was shorter in primary prevention group. 35% of decisions to implant were made before reaching referral centre When cardiac arrest was removed (as an indication for secondary prevention) there were no differences but statistics not shown.

Przybylski *et al*, 2005 (Poland)[136]	Yes (no statistical difference between primary vs. secondary	No	NR	NR	NR	No	Partially (limited analysis i.e. no survival analysis)	1 tertiary centre	Overall complications 33%. Inappropriate shocks in 30% (primary and secondary): infections: 4.3%, device failure 6.5%. No significant difference in complications rates between primary and secondary.	
Woo *et al*, 2007 (Canada)[140]	No	Yes	NR	NR	NR	No	Yes	1 tertiary centre	Inappropriate shocks (primary and secondary): 33% (or 10%/year);Device related fault, 13% (these patients were significantly younger than patients without lead complications (29 (14) vs. 48 (17) years; p=0.006).	Multivariate analysis identified two variables as significant predictors of inappropriate discharges: (a) age ,30 years at the time of ICD 8.0; p=0.03)) and (b) history of AF before ICD insertion (hazard ratio (HR)=3.0 (95% CI 1.1 to (HR=3.1 (95% CI 1.2 to 8.1); p=0.02).
Cha *et al*, 2007 (USA) [141]		No				No	Partially	1 tertiary centre	Inappropriate shocks (primary): 15% (9% of patient had >5) ; device related fault, %	Cox's regression model was univariate. It did not show differences between primary and secondary prevention group
Kaski *et al*, 2007 (UK)[137]	Yes	No	NR	Yes	Yes	No	NR	1 tertiary centre	Inappropriate shock (primary: 11.8%): infections, 4.5%: haematoma, 4.5%, one patient got depression /anxiety	