ESCAPE-HCM study: Evaluation of SScreening of Asymptomatic PatiEnts with Hypertrophic CardioMyopathy

Study design, objectives and expected results

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The ESCAPE-HCM study is a prospective follow-up study of asymptomatic mutation-carrying relatives of HCM patients aiming at optimising anamnestic and cardiological evaluation and surveillance for this group. All relatives undergo regular cardiological evaluation and risk status is prospectively estimated, according to known HCM-related risk factors for sudden cardiac death. (*Neth Heart J* 2007;15:216-20.)

Keywords: cardiomyopathy (hypertrophic), death (sudden) (cardiac), risk stratification, genetic

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac disease characterised by anatomic changes of the heart musculature and cardiac arrhythmias predisposing to sudden cardiac death (SCD) at a relatively young age. HCM is a relatively common genetic disease affecting at least 1 in 500 persons in the general population (32,000 persons in the Netherlands),¹⁻⁵ which is comparable to the prevalence of familial hypercholesterolaemia (FH).⁶ HCM is inherited in an autosomal dominant mode, which implies that 50% of first-degree relatives carry the disease-causing mutation. The risk of sudden cardiac death is approx-

imately 1% annually in unselected HCM patients, but increases to 5% or higher in high-risk patients.^{7,8}

DNA testing for HCM became possible in 1996. After routine mutation screening of the MYBPC3 gene became available in the Netherlands in 2003, the likelihood of detecting the disease-causing mutation in a proband with HCM increased from 10 to 50%. Of all HCM patients in the Netherlands in whom a mutation is detected, 35 to 40% carry one of the three Dutch founder mutations (c.2373_2374insG (25-30%),⁹ c.2827C>T or c.2864_2865delCT (10%)) in the MYBPC3 gene, a situation unique in the world. In the Netherlands, the current policy is that after detection of a mutation in the proband, relatives are invited by letter to attend the cardiogenetic outpatient clinic in a university hospital to discuss presymptomatic molecular or cardiological diagnostics. Almost all relatives who attend our clinics consent to presymptomatic DNA testing. When the familial mutation is detected in a relative, this mutation carrier is advised to undergo regular cardiological evaluation to detect potential left ventricular hypertrophy and to assess known risk factors for sudden cardiac death. Presymptomatic molecular and cardiological diagnostics supported by a stratification for risk of SCD are considered a valuable and promising approach to detect HCM early and to prevent SCD.¹⁰⁻¹³

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Rationale of the study

According to the ACC/ESC Consensus Report on HCM, all mutation carriers should be identified and regularly undergo cardiological evaluation, regardless of the presence of HCM-related symptoms.¹⁴ A large proportion of this group consists of patients with a low risk of sudden cardiac death and cardiological diagnostic tools for this group are far-reaching and burdensome. As about 25 to 35% of asymptomatic relatives develop a prognostic unfavourable course,¹⁰ all mutation carriers should regularly undergo cardiological evaluation. Preferably, we would like to identify this subgroup with a prognostically unfavour-

able course in an asymptomatic phase by risk stratification. Since more than 90% of Dutch mutation carriers still await identification, timely risk stratification could be helpful to optimise the efficiency of diagnostic care for all these patients. Risk stratification is based on the outcome of various cardiac function tests, medical history and family history (six risk factors according to the ACC/ESC Consensus Report (table 1)).¹⁴ According to this guideline a patient is considered at high risk when at least two out of six risk factors are present.

ESCAPE-HCM is designed to optimise care for these asymptomatic mutation carriers by risk stratification. The study has the following research questions: (1) Can the process of presymptomatic DNA testing, cardiological follow-up and treatment be optimised by identifying carriers with an initial low risk and carriers with an initial high risk of SCD? (2) Can the prognostic accuracy of the initial risk stratification be improved if relatives carry one of the three Dutch founder mutations (c.2373_2374insG, c.2827C>T or c.2864_2865delCT mutation in the MYBPC3 gene)?

Material and methods

Study design

ESCAPE-HCM is a multicentre prospective follow-up study. Patients from all the university hospitals in the Netherlands are invited to participate. Patients are seen in multidisciplinary cardiogenetic outpatient clinics at the university hospitals by a clinical geneticist and a cardiologist. All the university hospitals in the Netherlands are participating in this study. At this moment five centres are actively including patients.

Process of risk stratification

Relatives of a proband in whom a mutation has been detected in one of the genes associated with HCM are invited to visit a cardiogenetic outpatient clinic. Relatives who are found to have the familial mutation are advised to undergo regular (at least once biannually) cardiological evaluations, including an ECG, echocardiography, 24-hour ambulatory (Holter) ECG recording and an exercise test. Consecutively their first-degree relatives are invited to visit a cardiogenetic outpatient clinic and so on (principle of cascade screening).

Mutation carriers with a family history positive for SCD, successful resuscitation or appropriate discharge of an internal cardiac defibrillator (ICD) are considered at initial high risk and relatives without these risk factors are considered at an initial low risk. Cardiac evaluation can reveal one or more additional risk factors. Patients who are initially classified at high risk or low risk can finally be classified as high risk (at least two risk factors) if extra risk factors are discovered during the first cardiological screening or later during follow-up (figure 1). Follow-up of relatives consists of cardiological diagnostics at least biannually. The patients who are finally classified as high risk are at considerable risk for SCD and effective preventive measures (i.e. ICD implantation) should be considered.^{7,14-16}

In a literature study known and possible risk factors for SCD in HCM patients will be evaluated. Possible risk factors that prove to be of significant incremental value will also be taken into account in risk stratification in our study population. These possible risk factors are

Table 1. Known risk factors for SCD in HCM patients.¹⁴

Risk factor	Definition
1. Positive family history for premature sudden cardiac death	Unexpected nontraumatic death within one hour after the onset of symptoms and without previous severe symptoms <55 years, including unwitnessed unexpected nocturnal death in a relative. Including equivalents as successful reanimation or appropriate ICD discharge.
2. Prior cardiac arrest or sustained ventricular tachycardia	Cardiac arrest (VF) in history or spontaneously occurring sustained ventricular tachycardia.
3. Nonsustained ventricular tachycardia	One or more runs of ≥ 3 consecutive ventricular extrasystoles at a rate of more than 120 beats/min lasting for <30 seconds.
4. Extreme left ventricular hypertrophy	Maximum left ventricular wall thickness of ≥ 30 mm.
5. Abnormal blood pressure response during upright exercise	A failure of the systolic blood pressure to rise by >20 mmHg from baseline values, or a fall of >10 mmHg from the maximum blood pressure during upright exercise.
6. Unexplained syncope	≥ 2 episodes of unexplained syncope in the previous year.

Figure 1. Flowchart of risk stratification. FU=follow-up.

age, gender, left ventricular outflow tract obstruction, NYHA functional class III-IV and atrial fibrillation.

Patient eligibility

Inclusion criteria are:

- asymptomatic mutation-carrying relatives of HCM probands, in whom the familial mutation has been identified (asymptomatic at the moment of molecular diagnostics);
- age of at least 10 years (or younger if the diagnosis of HCM in a relative was made before the age of 10);
- informed consent.

The exclusion criteria are:

- relatives of HCM probands, in whom no disease-causing mutation could be identified;
- relatives of HCM probands who are already being treated for HCM;
- the presence of another inherited cardiac disease in the family predisposing to sudden cardiac death.

Assessment of prognosis

Outcome measures of this study are:

- a cardiac event (ventricular fibrillation, sudden cardiac death, appropriate ICD discharge, death due to heart failure or heart transplantation and overall mortality);
- final high-risk status (two or more risk factors).

The follow-up period is defined as the time interval between entering the study and the end of the study. The study started in January 2005. At this moment follow-up will end in January 2009 and is thus limited to a maximum of four years. We aim at continuing follow-up after the end of this study.

Power

Using a one-sample test with $\alpha=0.05$ (one-sided), $\beta=1-0.80$ and $p=0.05$ and an expected proportion of endpoint of 1%, a proportion of endpoints of 2% or higher can be excluded with 95% confidence if at least

Figure 2. Number of included patients (probands and relatives) per university hospital on 1 December 2006.

268 relatives in the initially low-risk group are included. Hence at least 420 relatives (initially high and low risk) have to be included in the study.

Administrative aspects

All known asymptomatic mutation carriers will be informed about the nature, relevance and consequences of the study. Newly diagnosed mutation carriers are informed by a clinical geneticist or genetic counsellor at the cardiogenetic outpatient clinic. Written informed consent is required for participation in this study.

Data analysis

Data are recorded and stored in the nationwide GENCOR database, an internet-based national database for all inherited cardiac diseases under the authority of the Interuniversity Cardiologial Institute of the Netherlands (www.gencor.nl).^{14,17} Collection and storage of data is done by an experienced database manager. Scoring of events and outcomes as indicated above will be done by a clinical event committee.

Analysis of the cumulative number of relatives with a final high-risk status distinguished by initially low-versus initially high-risk status, comparison of survival curves and sensitivity and specificity of initial risk stratification will be performed.

Timeline

The study period is limited to four years and will end in January 2009. Follow-up and enrolment of patients will continue after this period.

Additional analysis

The consequences of various diagnostic and treatment strategies for the carrier with respect to emotional burden, risk perception, quality of life and efficiency (cost effectiveness) will be evaluated. Data on the carriers emotional burden, risk perception and quality of life of the diagnostic and treatment strategies are obtained using questionnaires.

The aim of cost effectiveness is to compare the costs of two screening methods or strategies relative to the gain in health status achieved with these strategies. One method is application of the current ACC/ESC

guideline. The alternative strategy is the one that is based on the risk stratification described above with less frequent cardiological evaluation in low-risk patients. The main objective is to identify a subgroup of mutation carriers in whom the frequency of cardiological diagnostics may be safely reduced without compromising early detection and treatment of the disease.

Expected results

We expect risk stratification to be successful in indicating true low and high risk of SCD. This means that asymptomatic carriers with a low-risk status may need less frequent cardiological evaluation. Perhaps no presymptomatic diagnostics at all are possible for these relatives without an increase in the risk of SCD in this group. If proper initial risk stratification is impossible to achieve, all carriers of HCM-causing mutations will have to be identified in the coming years and advised to have regular cardiological follow-up. This will imply a considerable workload for the departments of clinical genetics and cardiology, and pose a major financial burden to the health care system and may severely compromise psychosocial health for individuals.

On 1 December 2006 we had received informed consent for participation from 457 mutation-carrying probands and relatives from five university hospitals (figure 2). About two thirds of these participants are asymptomatic relatives. About 50% of the included families have a history of SCD in their family. At this moment the data of 114 mutation carriers have been entered into the GENCOR database (table 2).

Table 2. Clinical characteristics of 114 hypertrophic cardiomyopathy mutation carriers.

Age (years)	45.7±17.4
Male sex	55 (48.3%)
Relative	72 (63.2%)
Clinical diagnosis of HCM	65 (57.0%)
Age at diagnosis (years)	37.3±15.8

Data are presented as the mean value±SD or number (%) of patients.

Consequences for current practice

The study results depend on cardiological evaluation of the risk status of all mutation carriers. At this moment there is no consensus about the frequency of cardiological evaluation, but current practice is that every mutation carrier is evaluated once every one to two years. Cardiological evaluation should comprise the following clinical assessments: careful personal and family history; noninvasive testing with two-dimensional echocardiography; 24- or 48-hour ambulatory (Holter) ECG recording and blood pressure response during maximal upright exercise (treadmill or bicycle).¹⁴ This also holds for older asymptomatic mutation carriers.

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Appendix 1. Members of the ESCAPE-HCM study group.

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