Hypertrophic cardiomyopathy: towards an optimal strategy
Christiaans, I.

Citation for published version (APA):
Christiaans, I. (2010). Hypertrophic cardiomyopathy: towards an optimal strategy

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
ESCape-HCM: Evaluation of Screeening of Asymptomatic PatiEnts with Hypertrophic CardioMyopathy

2.2 Risk factors for sudden cardiac death and follow-up in a large nationwide cohort of predictively tested hypertrophic cardiomyopathy mutation carriers.


Submitted
Abstract

Aims
We investigated the presence of a clinical diagnosis of hypertrophic cardiomyopathy (HCM), risk factors for sudden cardiac death (SCD), and cardiac events during follow-up in all known Dutch predictively tested asymptomatic carriers of a sarcomeric gene mutation.

Methods and results
136 (30%) of 447 mutation carriers were diagnosed with HCM at one or more cardiological evaluation(s). Kaplan-Meier curves suggested slower progression to manifest HCM in carriers <40 years. Male gender (hazard ratio 1.69 [95%-confidence interval 1.20-2.37]) and age (hazard ratio per year 1.02 [95%-confidence interval 1.01-1.03]) were independent predictors for manifest disease. Twenty-three percent of carriers, with and without manifest disease, had established risk factor(s) for SCD (no significant difference). During an average follow-up of 3.5±1.7 years, two carriers, both with manifest disease, died suddenly (0.13%/person-year). This low event rate hampered prognostic evaluation of risk factors for SCD. A high risk status for SCD (≥2 risk factors and manifest HCM) was present in 17 carriers during follow-up (1.1%/person-year). Age proved to be a small but significant predictor for a high risk status for SCD.

Conclusion
Thirty percent of carriers had or developed manifest HCM after predictive DNA testing. Older age and male gender were independent predictors for manifest disease. Risk factors for SCD were frequently present. Our data suggest that SCD risk is low and risk stratification for SCD can be omitted in carriers without manifest disease and that frequency of cardiological evaluations can be decreased in carriers <40 years as long as hypertrophy is absent.
Risk stratification for SCD in follow-up

Introduction
Hypertrophic cardiomyopathy (HCM) is a common genetic disease associated with an increased mortality due to heart failure, trombo-embolic complications and sudden cardiac death (SCD). Several factors associated with an elevated risk of SCD in HCM patients have been identified.² The risk of SCD is approximately 1% annually in patients with manifest HCM but increases to 5% annually or more if risk factors for SCD are present.¹, ² It has been proposed that in patients with ≥ 1 risk factor the implantation of an internal cardioverter defibrillator (ICD), a therapy with proven efficacy in the prevention of SCD, should be considered, and in patients with ≥ 2 risk factors should be advised.³-⁶

Mutations in sarcomeric genes are identified in approximately 50% of HCM patients.⁷ After identification of a pathogenic mutation in an HCM patient (the proband), relatives can be identified or excluded as mutation carrier by means of predictive genetic testing (cascade screening). Proven mutation carriers should be referred for regular cardiological evaluation according to the ACC/ESC consensus document, including risk stratification for SCD.³ As predictive molecular testing is not yet widespread, most countries restrict risk stratification for SCD to relatives who are found to have manifest disease on echocardiography. Therefore, in relatives carrying the familial mutation not much is known about: (1) the risk of developing manifest HCM, (2) the presence and development of risk factors for SCD, and (3) the association of these risk factors with an increased risk of SCD. This hampers optimal management of mutation carrying relatives.

This study reports the results of systematic follow-up in a large group of asymptomatic relatives with a proven familial mutation in one of the sarcomeric genes identified through cascade screening. We address the presence of a clinical diagnosis of HCM, of risk factors for SCD during follow-up and their associations with cardiac events.

Methods

Patients
From families with a putative pathogenetic mutation in the MYBPC3, MYH7, TNNT2, TPM1 or MYL2 gene, we included relatives, carrying the familial mutation, who were asymptomatic –if symptoms (e.g. chest pain, palpitations) were present they had been insufficient to consult a physician- and without a clinical diagnosis of HCM at the time of DNA-testing. Probands and relatives who had been clinically diagnosed with HCM before genetic testing were excluded. Genetic counselling and testing of (probands and) these relatives is only provided by University Hospitals in the Netherlands. All eight Dutch University Hospitals included mutation carriers. Predictive genetic testing of children was advised from the age of 10, although exceptionally children have been tested at younger age (n=12 in our cohort). All included mutation carrying relatives (or their parents) provided written informed consent for anonymous scientific use of their data.

Mutation carrying relatives were included in this prospective cohort study from 2001 when the first asymptomatic relatives were identified as mutation carrier through cascade screening until December 2008. Because of the increasing number of HCM patients in whom DNA-diagnostics is performed and the subsequent cascade screening of the relatives, the inclusion of asymptomatic relatives also shows an increase in time.
Data
From all mutation carriers a family history was recorded with information on SCD in relatives up to the third degree. Carriers were advised to regularly undergo cardiological evaluation including complete risk stratification with an ECG, echocardiogram, 24-hour ambulatory Holter recording, and an exercise test. Clinical parameters from all their cardiological evaluations (often performed in local hospitals) after predictive genetic testing were recorded. In adults a clinical diagnosis of HCM was made when on echocardiography the maximal left ventricular wall thickness was ≥ 13mm and/or severe systolic anterior movement of the mitral valve (SAM) was present. In children <16 years the clinical diagnosis was made when on echocardiography a maximal wall thickness ≥ 2 SD for their body surface area was present.

The following risk factors for SCD were assessed:
1) Family history of premature sudden cardiac death. Unexpected non-traumatic premature death within one hour after the onset of symptoms and without previous severe symptoms in (a) relative(s), including unwitnessed unexpected nocturnal death and equivalents like successful resuscitation or appropriate ICD discharge. With respect to the age and degree of kinship and number of the relative(s) involved, we use the definition most used in literature: 2 relatives with SCD < 40 years.
2) Unexplained syncope. Unexplained syncope, judged not to be neurocardiogenic.
3) Non-sustained ventricular tachycardia (NSVT). One or more runs of 3 or more consecutive ventricular extrasystoles at a rate of more than 120 beats per minute lasting for less than 30 seconds at exercise test or 24-hour ambulatory Holter recording.
4) Extreme left ventricular hypertrophy. Maximum left ventricular wall thickness of 30 mm or more on echocardiography.
5) Abnormal blood pressure response (ABPR) during upright exercise. A failure of the systolic blood pressure to rise by more than 20 mm Hg from baseline values, or a fall of more than 10 mm Hg from the maximum blood pressure during upright exercise (treadmill Bruce protocol or bicycle protocol).

The cumulative number of risk factors is the number of the above mentioned five risk factors for SCD that are positive. Carriers were defined to be at high risk for SCD when manifest HCM and ≥ 2 risk factors for SCD were present or when they had previously experienced an aborted cardiac arrest (ventricular fibrillation) or sustained ventricular tachycardia (VT).

Duration of follow-up since the DNA test result was on average (±SD) 3.5±1.7 years. Outcome measures during follow-up were a clinical diagnosis of HCM, death, cardiovascular death, SCD, heart transplantation, and appropriate ICD discharge. As a proxy outcome for SCD we used a high risk status for SCD.

Genetic analysis
Mutation analysis in probands was performed according to a previously published protocol. Nonsense or frameshift mutations were considered to be pathogenic based on descriptions in literature, cosegregation with the phenotype, absence in at least 200 ethnically matched controls, the predicted probability of nonsense-mediated mRNA decay and the results of functional assays. Missense mutations were defined as (probably) pathogenic based on descriptions in literature, cosegregation with the phenotype, absence in at least 200 controls, evolutionary conservation of the amino acid, and chemical differences between the involved amino acids.
Risk stratification for SCD in follow-up

Statistical analysis

Data were analysed with SPSS (version 15.0) statistical software. Data are expressed as means (SD) or as a frequency. Student’s t-test or one way ANOVA was used for the comparison of normally distributed continuous variables, non-parametric methods for not-normally distributed continuous variables and Pearson’s χ² for comparisons between dichotomous or categorical variables. Survival analysis was used to describe the relationship between the presence of outcome measures and clinical variables during follow-up. Carriers were censored when information on that specific outcome was no longer available. Figures show cumulative incidence until inclusive the last event. The magnitude of the risk (hazard ratios) associated with the presence of clinical variables was calculated using Cox regression analysis with a 95% confidence interval. Hazard ratios were calculated for variables significantly associated with the

Table 1. Clinical parameters of 447 mutation carrying relatives at first cardiological evaluation.
following (proxy) outcome measures: a clinical diagnosis of HCM, death, SCD, and appropriate ICD discharge. The variables age and gender were always included. We expected some of our outcome measures to be very infrequent, which could hamper prognostic evaluation. Therefore as a proxy outcome measure for our main outcome, SCD, we used a high risk status for SCD. For this proxy outcome measure, however, hazard ratios of (a) risk factors for SCD and (b) the presence of a clinical diagnosis of HCM could not be evaluated even when they were significantly associated since they are part of this proxy outcome measure (circularity). A \( P \)-value \(<0.05\) (two-sided) was considered significant.

**Results**

**First cardiological evaluation**

In the period between 2001 and 2008, 447 asymptomatic relatives were identified as mutation carrier. Table 1 displays their clinical parameters at first cardiological evaluation. Clinical parameters at first evaluation from part of the carriers have been published.\(^{13, 14}\) Mean age (±SD) of carriers was 39.3±17.6 (range 1-86) years and 195 (44%) were male. At first cardiological evaluation a diagnosis of HCM was made in 107 (24%) carriers. Risk factors for SCD were frequently present; 33% of all carriers had one or more risk factors (29% had one risk factor, 4% had more risk factors).

Differences between carriers with versus those without a clinical diagnosis of HCM at first cardiological evaluation are displayed in Table 1. Carriers in whom a clinical diagnosis of HCM was made at first evaluation were significantly older than carriers in whom hypertrophy was absent at that time (45.4±17.8 vs. 37.6±18.0 years, \( P \)-value \(<0.001\)) and were more often of male gender (57.0\% vs. 39.4\%, \( P \)-value 0.001). Extreme left ventricular hypertrophy was by definition only present in carriers with a clinical diagnosis of HCM. NSVT was significantly more often detected during Holter recordings in carriers with a clinical diagnosis of HCM (\( P \)-value \(<0.001\)), irrespective of their age. There was no significant difference in the cumulative number of risk factors between carriers with and without a clinical diagnosis of HCM.

Risk stratification for SCD was incomplete in 41\% of mutation carriers at first cardiological evaluation. The risk factors ABPR and NSVT were evaluated in only 66\% and 71\% of carriers, respectively. There were no significant associations between clinical characteristics and incomplete risk stratification, except for the mutated gene, the presence of NSVT, and the cumulative number of risk factors. Risk stratification was more often incomplete in TNNT2 gene mutation carriers compared to carriers of a mutation in another gene (\( P \)-value \(<0.001\)). Surprisingly, NSVT was significantly more frequently registered in carriers with incomplete risk stratification compared to carriers with complete risk stratification (14\% vs. 6\% respectively, \( P \)-value 0.035). As expected, the cumulative number of risk factors for SCD was significantly higher in carriers who had been evaluated for all risk factors (\( P \)-value 0.002). Twenty-four percent of carriers with incomplete risk stratification had ≥ 1 risk factor for SCD compared to 39\% of the carriers who had been completely evaluated.

**Cardiological evaluation during follow-up**

239 mutation carriers were evaluated by cardiac-function testing more than once during follow-up (Table 2). Between first and last evaluation of these 239 carriers (average (±SD) duration: 2.5±1.5 years) the percentage of clinically diagnosed carriers increased from 32\% to 44\% (\( P \)-value 0.011) and more carriers were evaluated for all risk factors (61\% at first evaluation...
Risk stratification for SCD in follow-up

and 75% at last evaluation, P-value <0.001). The cumulative number of risk factors also increased with more carriers having one or more risk factors at last cardiological evaluation, but this increase in risk factors was not significant. Eventually, 25 carriers (of whom 16 with manifest HCM) had or developed ≥ 2 risk factors for SCD. Eighteen carriers had an ICD implanted: 6 had a high risk status for SCD, and the remaining 12 were regarded by their cardiologist as patients with a high risk as they carried a TNNT2 mutation previously described as malignant (n=4), had manifest HCM and 1 risk factor for SCD and SCD in their relatives but insufficient to meet our definitions (n=5), had extreme LVH (n=1), and had manifest HCM and SCD in close relatives but insufficient to meet our definitions (n=2).

We also compared clinical characteristics at first evaluation between carriers who did not receive additional cardiological evaluations and carriers who did. As expected, a clinical diagnosis of HCM was more often present (P-value <0.001) and the cumulative number of risk factors was higher (P-value 0.021) at first evaluation in carriers who had been evaluated more than once.

During the average (±SD) follow-up time of 3.5±1.7 years four (0.9%) mutation carriers died (mortality rate of 0.25% per person-year). Two died of non-cardiovascular causes and two (0.4%) died unexpectedly (SCD rate of 0.13% per person-year). One was a female who died at the age of 80 years with documented VF. She had been diagnosed with HCM at the first evaluation at age 76 and had no risk factors for SCD, but both NSVT and ABPR had never been evaluated. The other unexpected death was a man of 59 years who died during his sleep and who had had no complaints the previous day. He had been diagnosed with HCM at the first cardiological evaluation at age 58. He had one risk factor for SCD; NSVT was present during Holter recording and exercise testing. We regard both unexpected deaths as SCD. None of the

<p>| Table 2. Clinical parameters of 239 mutation carriers with more than one cardiological evaluation at first and last cardiological evaluation. |</p>
<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Mutation carriers with 1 cardiological evaluation (n=208)</th>
<th>Mutation carriers with &gt;1 cardiological evaluation (n=239)</th>
<th>Mutation carriers with &gt;1 cardiological evaluation (n=239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis of HCM</td>
<td>32 (208, 15.4%)††</td>
<td>76 (239, 31.8%)</td>
<td>104 (239, 43.5%)*</td>
</tr>
<tr>
<td>Risk factors for SCD</td>
<td>Extreme left ventricular hypertrophy</td>
<td>1 (208, 0.5%)</td>
<td>3 (239, 1.3%)</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>6 (144, 4.2%)†</td>
<td>18 (175, 10.3%)</td>
<td>29 (206, 14.1%)</td>
</tr>
<tr>
<td>Abnormal blood pressure response</td>
<td>13 (131, 9.9%)†</td>
<td>31 (166, 18.7%)</td>
<td>31 (166, 18.7%)</td>
</tr>
<tr>
<td>Previous cardiac arrest or VT</td>
<td>1 (208, 0.5%)</td>
<td>0 (239, 0.0%)</td>
<td>0 (239, 0.0%)</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>4 (208, 1.9%)†</td>
<td>15 (239, 6.3%)</td>
<td>15 (239, 6.3%)</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>35 (208, 16.8%)</td>
<td>38 (239, 15.9%)</td>
<td>38 (239, 15.9%)</td>
</tr>
<tr>
<td>All risk factors evaluated</td>
<td>118 (208, 56.7%)</td>
<td>145 (239, 60.7%)</td>
<td>180 (239, 75.3%)***</td>
</tr>
<tr>
<td>Number of risk factors for SCD</td>
<td>0 risk factors</td>
<td>149 (208, 71.6%)†</td>
<td>150 (239, 62.8%)</td>
</tr>
<tr>
<td>1 risk factors</td>
<td>58 (208, 27.9%)</td>
<td>73 (239, 30.5%)</td>
<td>83 (239, 34.7%)</td>
</tr>
<tr>
<td>≥ 2 risk factors</td>
<td>1 (208, 0.5%)</td>
<td>16 (239, 6.7%)</td>
<td>25 (239, 10.5%)</td>
</tr>
</tbody>
</table>

Data are means±SD or number and proportion (%). Mean F-U until last cardiological evaluation 2.5±1.52 years. Significant differences between carriers with follow-up at first and at last evaluation: †P-value <0.05. **P-value <0.001. Significant differences between carriers without follow-up and carriers with follow-up at first evaluation: ††P-value <0.05. †††P-value <0.001.

HCM, Hypertrophic Cardiomyopathy; SCD, sudden cardiac death; VT, ventricular tachycardia.
**Figure 1.** Clinical diagnosis of HCM and high risk status for SCD (manifest HCM and ≥ 2 risk factors) during follow-up.

**Figure 2.** Clinical diagnosis of HCM during follow-up in mutation carriers from different age categories.

**Figure 3.** Clinical diagnosis of HCM during follow-up in mutation carriers from different age categories not diagnosed with manifest HCM at first cardiological evaluation.
Risk stratification for SCD in follow-up
carriers received a heart transplantation and appropriate ICD discharge did not occur in the 18 carriers who had an ICD implanted. A high risk status for SCD, our proxy outcome measure for SCD, was present in 17 (3.8%) carriers during follow-up (1.1% per person-year).

**Kaplan Meier analysis and hazard ratios**

In total, 136 (30%) mutation carriers were diagnosed with HCM at first cardiological evaluation or during follow-up. A clinical diagnosis of HCM was made after 4.5 years of follow-up in 50% of carriers (95%-CI: 2.7-6.3 years) (Figure 1).

The presence of a clinical diagnosis in time (disease penetrance) differed by gender and age. In male carriers 50% had a clinical diagnosis after 2.5 years, whereas in female carriers 50% had a clinical diagnosis only after 5.4 years of follow-up (P-value 0.002). Initial Kaplan-Meier analysis for age in six different age categories with almost similar numbers of carriers (<15, 15-30, 30-40, 40-50, 50-65 and >65 years) showed overlapping curves in some age categories. Age categories with similar disease penetrance were joined, resulting in a significantly different disease penetrance in the age categories <40, 40-65, and >65 years (Figure 2). Fifty-percent of carriers had a clinical diagnosis after 7.2, 2.3 and 0.5 years of follow-up respectively. Since manifest disease could have been present long before the first cardiological evaluation, we also assessed disease penetrance in the 163 carriers who had no clinical diagnosis at first cardiological evaluation and received at least one further cardiological evaluation (Figure 3). During a follow-up of 3 years after the first cardiological evaluation, 12.8% of carriers aged <40 years developed HCM, 31.3% of carriers aged between 40-65 years and 33.3% of carriers aged >65 years.

Both gender and age were independent predictors for a clinical diagnosis of HCM (Table 3). Male carriers had a 1.69 higher probability of a clinical diagnosis of HCM (95%-CI: 1.20-2.37, P-value 0.003). The probability of a diagnosis of HCM increased 1.02 per year increase in age (95%-CI: 1.01-1.03). The multivariate model including gender and age category (<40, 40-65 and >65 years) had the same fit as the model including age as a continuous variable and shows the relative risk of age with a multivariate hazard ratio of 1.77 for age category (Table 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95%-CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: clinical diagnosis of HCM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender-UV</td>
<td>1.69</td>
<td>1.20-2.38</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Age (years)-UV</td>
<td>1.02</td>
<td>1.01-1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age category*-UV</td>
<td>1.83</td>
<td>1.44-2.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender-MV</td>
<td>1.69</td>
<td>1.20-2.37</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Age (years)-MV</td>
<td>1.02</td>
<td>1.01-1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender-MV</td>
<td>1.62</td>
<td>1.15-2.28</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Age category* -MV</td>
<td>1.77</td>
<td>1.40-2.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Outcome: high risk status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender-UV</td>
<td>0.63</td>
<td>0.23-1.70</td>
<td>0.355</td>
</tr>
<tr>
<td>Age (years)-UV</td>
<td>1.03</td>
<td>1.00-1.06</td>
<td><strong>0.026</strong></td>
</tr>
<tr>
<td>Age category* -UV</td>
<td>2.22</td>
<td>1.12-4.41</td>
<td><strong>0.022</strong></td>
</tr>
</tbody>
</table>

HR: hazard ratio; CI: confidence interval; UV: univariate; HCM: hypertrophic cardiomyopathy; SCD: sudden cardiac death; MV: multivariate
* Age categories were <40, 40-65, and >65 years.

Table 3. Hazard ratios of gender, manifest disease and age for different outcomes.
Although our aim was to estimate the hazard ratios of the clinical parameters and risk factors for SCD on the outcome measures death and SCD, the low number of deaths (n=4) and SCDs (n=2) prevented us to do so. Only age was significantly associated with a high risk status for SCD and not part of the definition of this proxy outcome measure. During follow-up, 17 mutation carriers developed a high risk status for SCD (Figure 1). Age, but not gender, proved to be a significant predictor for a high risk status of SCD (Table 3).

Discussion

A considerable proportion of asymptomatic HCM mutation carriers identified after predictive genetic testing had manifest HCM at first cardiological evaluation or developed manifest disease during follow-up. Penetrance of manifest HCM is known to be age dependent and HCM is detected more often in males.10, 15-17 This is also shown by our data because older age and male gender were independent risk factors for developing manifest HCM. The overrepresentation of males with a clinical diagnosis of HCM in the literature and in this study could also in part be due to the fact that diagnostic echocardiographic criteria are not adjusted for body surface area, which is in general smaller in females.

Risk factors for SCD were frequently present both in predictively tested carriers both with and without manifest disease. A majority (53%) of the carriers was evaluated cardiological more than once. These carriers had significantly longer follow-up –they had received their DNA test longer ago-, increasing the likelihood of an additional evaluation. A recent study of our group, however, showed that a considerable proportion of carriers received no cardiological follow-up because the cardiologist deemed follow-up unnecessary or because first evaluation showed no manifest disease.18 The present study also demonstrated that carriers who received additional evaluations more often had manifest disease and a higher number of risk factors. Likely, the presence of risk factors and hypertrophy are reasons for the cardiologist for further evaluation, since they are associated with an unfavourable prognosis in HCM patients in literature.

The prognostic impact of risk factors for SCD in HCM patients (i.e. with manifest disease) has been confirmed in many studies and they can therefore be used in risk stratification in mutation carriers with manifest disease. However, it is still unclear if these risk factors are also associated with SCD in mutation carriers without manifest disease, although SCD has been described in this group.19 Due to the low incidence of SCD in our study, we were unable to evaluate the prognostic impact of these risk factors on SCD. While our study with medium-term follow-up suggests that the risk of SCD is probably small in this population, a longer follow-up is needed to draw more definite conclusions. The low risk of SCD in our cohort may also be the result of selection bias. Since relatives or mutation carriers with an unfavourable prognosis are either dead or diagnosed with manifest disease because of symptoms and therefore excluded from this study, predictively tested mutation carriers at study onset are probably more likely to be healthy or asymptomatic until they were tested at a mean age of 39 years and probably have a relatively favourable prognosis.

Since the risk of SCD in predictively tested carriers is probably very low, one could argue that intensive cardiological evaluation including risk stratification as recommended in international guidelines is unnecessary. The guidelines recommend yearly evaluation including risk stratification for SCD when HCM is manifest. In mutation carriers without manifest HCM it is recommended to also include risk stratification preferably on a yearly basis. As SCD occurred only twice, both times in carriers with manifest HCM, our study suggests that risk stratification
Risk stratification for SCD in follow-up

for SCD may be omitted as long as HCM is not yet manifest. Our results on the clinical diagnosis of HCM in time (disease penetrance) in mutation carriers provide more insight in the optimal frequency of cardiological evaluations. The penetrance of a clinical diagnosis of HCM during follow-up after the first cardiological evaluation differs per age group, with less carriers per year developing HCM under the age of 40 years (Figure 3). It is unlikely that this is due to the screening interval, since this is not different from that in the other age categories. Our data therefore suggest that in carriers <40 years without hypertrophy at first evaluation hypertrophy develops more slowly. Therefore we propose to decrease the frequency of cardiological evaluations to, for example, once every two years in mutation carriers <40 years without manifest disease. Our data also show that HCM can still become manifest at higher age and that cardiological evaluations should therefore continue until advanced age.

Study limitations
Although our group of mutation carriers is of considerable size, distribution of a few characteristics was skewed. Significantly less men than women were included. This could be due to the fact that males are more often affected, and affected relatives and probands were excluded from this study. Most carriers had a mutation in the MYBPC3 gene. Although there was no association between the mutated gene and outcome measures, definite genotype-phenotype correlations with respect to age of diagnosis and risk factors for SCD cannot be made and it is uncertain if our results can be generalised to predictively tested carriers of a mutation in other sarcomeric genes. Mutations in the MYBPC3 gene, however, are worldwide one of the most frequent causes of HCM, accounting for about 30% of all identified HCM mutations.

Unfortunately not all mutation carriers received a Holter recording and/or exercise test at first cardiological evaluation. Other studies show that complete stratification of all six risk factors is not customary practice in HCM patients, not to mention the practice in asymptomatic HCM mutation carriers. Complete risk stratification was significantly less often performed in carriers of a TNNT2 gene mutation compared to carriers of other mutated genes. This is probably due to the fact that in five of the 20 TNNT2 gene mutation carriers the mutation (R92W) has been described as very malignant with respect to the incidence of SCD. For this reason they immediately received an ICD and remaining risk factors for SCD were not further evaluated. Because one or more risk factors were less often present in the carriers without a complete evaluation of risk factors, it seems likely that the cumulative number of risk factors for SCD as found in the entire cohort is underestimated. Other clinical characteristics were not associated with completeness of risk stratification making selection bias unlikely.

Predictive genetic screening occurred in tertiary care centres. Because this is the only setting where genetic testing for HCM is possible in the Netherlands, we do not expect selection bias based upon the type of centre.

With the current follow-up and population size the incidence of SCD is too small to draw meaningful conclusions on the prognostic significance of risk factors for SCD in this group of asymptomatic mutation carriers.

Conclusions
Of the mutation carrying relatives, 107 (24%) had manifest HCM at first cardiological evaluation, which increased to 30% during follow-up. Older age and male gender were independent risk factors for manifest disease. Manifest HCM appears to develop more slowly in carriers
<40 years, allowing less frequent cardiological evaluations (for example biannually instead of annually) in this age group as long as hypertrophy is absent.

One or more risk factors for SCD were present in 33% of carriers at first evaluation. Seventeen (3.8%) carriers had a high risk status at first evaluation or during follow-up. The low SCD event rate suggests that the risk of SCD is very low in asymptomatic mutation carriers especially when disease is not manifest yet. Risk stratification for SCD could therefore probably be omitted in HCM mutation carriers as long as manifest disease is absent.

Our results suggest that the SCD event rate in asymptomatic mutation carrying relatives is lower than in probands, and that the ACC/ESC recommendations need revision to accommodate for mutation carrying relatives, i.e. the recommended screening policy appears unnecessary intensive and frequent.

Prolonged follow-up is needed to 1) evaluate the prognostic impact of risk factors for SCD, and 2) to determine the optimal screening policy (risk stratification, screening interval) in asymptomatic mutation carrying relatives.
References

21. Van Driest SL, Vasile VC, Ommen SR, et al. Myosin binding protein C mutations and compound heterozygosity...
