Manifest disease, risk factors for sudden cardiac death, and cardiac events in a large nationwide cohort of predictively tested hypertrophic cardiomyopathy mutation carriers: determining the best cardiological screening strategy

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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 predictively tested—not known to have a clinical diagnosis of HCM before the DNA test—carriers of a sarcomeric gene mutation and associations with age and gender to determine the best cardiological screening strategy.

Methods and results

One hundred and thirty-six (30%) of 446 mutation carriers were diagnosed with HCM at one or more cardiological evaluation(s). Male gender and higher age were associated with manifest disease. Incidence of newly diagnosed manifest HCM was <10% per person-year under the age of 40 years and >10% in older carriers, although numbers were small in carriers <15 years. 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% per person-year). A high-risk status for SCD (≥2 risk factors and manifest HCM) was present in 17 carriers during follow-up (2.4% per person-year). Age but not gender was associated with a high-risk status for SCD.

Conclusion

Thirty percent of carriers had or developed manifest HCM after predictive DNA testing and risk factors for SCD were frequently present. Our data suggest that the SCD risk is low and risk stratification for SCD can be omitted.

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Introduction

Hypertrophic cardiomyopathy (HCM) is a common genetic disease associated with an increased mortality due to heart failure, thrombo-embolic complications, and sudden cardiac death (SCD). Several factors associated with an elevated risk of SCD in HCM patients have been identified. The risk of SCD is ~1% annually in patients with manifest HCM but increases to 5% annually or more if risk factors for SCD are present. 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.

Mutations in sarcomeric genes are identified in ~50% of HCM patients. 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. 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: (i) the risk of developing manifest HCM, (ii) the presence and development of risk factors for SCD, and (iii) 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 relatives with a proven familial mutation in one of the sarcomeric genes identified through cascade screening. These relatives were predictively tested; they were not known to have manifest disease on echocardiography. Therefore, in relatives carrying the familial mutation, not much is known about: (i) the risk of developing manifest HCM, (ii) the presence and development of risk factors for SCD, and (iii) the association of these risk factors with an increased risk of SCD. This hampers optimal management of mutation-carrying relatives.

Methods

Population

In HCM, families with a disease-causing mutation predictive genetic testing can give more certainty than electrocardiogram (ECG) and echocardiography about which relatives are at risk of developing HCM and which relatives are not. As genetic testing excludes the relatives identified as non-carrier from cardiological follow-up, in the Netherlands genetic testing of relatives is performed before cardiological testing. We included relatives, carrying the familial mutation, who were not known to have a clinical diagnosis of HCM at the time of DNA testing (i.e. predictive genetic testing). Almost all included mutation carriers had not been cardiologicaly evaluated before the DNA test. Probands, affected relatives, and relatives not carrying the familial mutation were excluded. All included mutation-carrying relatives provided written informed consent for anonymous scientific use of their data.

We identified 446 mutation-carrying relatives came from 166 families with a putative pathogenic mutation in the MYBPC3, MYH7, TNNT2, TPM1, or MYL2 gene. The distribution of the mutated genes in the relatives was similar as in the probands. DNA analysis was performed according to a previously published protocol. Genetic counselling and testing of (probands and) relatives are only provided by University Hospitals in the Netherlands. All eight Dutch University Hospitals included mutation carriers. Uptake of predictive genetic testing in part of these families has been previously described and was 39% in the first year after identification of the causal mutation. In first-degree relatives, the percentage of carriers was 50.6% following autosomal dominant inheritance.

Data

From all predictively tested mutation-carrying relatives, a family history was recorded with the 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 h 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.

The HCM phenotype was assessed using echocardiography. In adults, a clinical diagnosis of HCM was made when on echocardiography the maximal left ventricular wall thickness was ≥13 mm and/or severe systolic anterior movement of the mitral valve 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:

(i) Family history of premature SCD. Unexpected non-traumatic premature death within 1 h after the onset of symptoms and without previous severe symptoms in (a) relative(s), including un-witnessed unexpected nocturnal death and equivalents such as 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 the literature: two relatives with SCD <40 years.

(ii) Unexplained syncope. Unexplained syncope, judged not to be neurocardiogenic.

(iii) Non-sustained ventricular tachycardia (NSVT). One or more runs of ≥3 consecutive ventricular extrasystoles at a rate of ≥120 b.p.m.
lasting for <30 s at exercise test or 24 h ambulatory Holter recording.

(iv) Extreme left ventricular hypertrophy. Maximum left ventricular wall thickness of ≥30 mm on echocardiography.

(v) Abnormal blood pressure response (ABPR) 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 (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).

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. All included carriers had at least one cardiological evaluation. Information on mortality was retrieved from the central Dutch Community Registration, and in case of death the cause of death was retrieved by contacting the general practitioner or the Dutch Bureau of Statistics.

Predictively tested carriers were included in this prospective cohort study from 1999 when the first relative was 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 predictively tested mutation-carrying relatives also shows an increase in time. Follow-up on mortality related outcome measures (death, cardiovascular death, SCD) ended in May 2009.

Statistical analysis

Data are expressed as mean (SD) or as a frequency, where appropriate. Comparison of subgroups for continuous and categorical variables was performed using linear and logistic regression, respectively. For all models, the generalized estimating equations method was used to correct for correlations between carriers due to family relations.

For all carriers, the times from birth to HCM diagnosis and to high-risk status for SCD were calculated, as well as from time of DNA diagnostics. For time to a clinical diagnosis of HCM and time to a high-risk status for SCD, carriers without a clinical diagnosis of HCM or without a high-risk status for SCD, respectively, were censored at the date of the last cardiological evaluation. For carriers without a clinical diagnosis of HCM at the first cardiological evaluation, follow-up to a clinical diagnosis of HCM and a high-risk status for SCD were calculated starting at the date of first cardiological evaluation.

Kaplan–Meier curves were calculated for time to a clinical diagnosis of HCM and time to a high-risk status for SCD for all carriers, with/without stratification by sex. All analyses were carried out using SPSS (version 15.0). P-values < 0.05 (two-sided) were considered significant.

Results

First cardiological evaluation

In the period between 2001 and 2008, 446 relatives were identified as mutation carrier by predictive DNA testing. Clinical parameters at first evaluation from part of the carriers have been published. Mean age (±SD) of carriers was 39.3 ± 17.6 (range 1–86) years and 195 (44%) were male. Although all carriers were not known to have a clinical diagnosis of HCM and most had not been cardiological evaluated before the predictive DNA test, at first cardiological evaluation a clinical 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; Table 1).

Differences between carriers with vs. 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. 37.4 ± 17.6 years, P-value < 0.001) and were more often of male gender (57.0 vs. 39.5%, P-value = 0.002). Extreme left ventricular hypertrophy was by definition only present in carriers with a clinical diagnosis of HCM. Non-sustained ventricular tachycardia was significantly more often detected during Holter recordings in carriers with a clinical diagnosis of HCM (P-value = 0.002), although this difference was not significant in carriers <50 years. 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 cumulative number of risk factors. 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 = 0.017). Twenty-four percent of carriers with incomplete risk stratification had ≥1 risk factor for SCD compared with 39% of the carriers with complete evaluation.

Cardiological evaluations during follow-up

In the entire cohort (n = 446), the average follow-up time from birth to the last cardiological evaluation was 39.8 ± 17.6 years (range 1.4–86.7). In the carriers without a clinical diagnosis of HCM at the first cardiological evaluation (n = 239), average follow-up time from birth to last cardiological evaluation was 38.0 ± 15.5 years (range 8.7–82.7). Duration of follow-up in all 446 carriers from date of the DNA test result onwards on mortality related outcome measures was on average (±SD) 3.5 ± 1.7 years (range 0–9.8 years). Duration of follow-up from date of the DNA test result onwards on cardiological evaluated outcome measures (clinical diagnosis of HCM, heart transplantation, appropriate ICD discharge) ended at the time of last cardiological evaluation and was on average (±SD) 1.7 ± 1.7 years (range 0–9.2 years), as only 238 carriers had more than one cardiological evaluation. None of the carriers was lost to follow-up.

Two hundred and thirty-eight mutation carriers were evaluated by cardiac function testing more than once during follow-up (Table 2, Figure 1). Between first and last evaluation [average (±SD) duration: 2.9 ± 1.6 years; range 0.2–9.2 years], the percentage of clinically diagnosed carriers increased from 32 to 44%
had or developed ≥tually, 25 of these 238 carriers (of whom 16 with manifest HCM) increased, but this increase in risk factors was not significant. Even-
a high risk as they carried a \textit{TNNT2}
remaining 12 were regarded by their cardiologist as patients with
an ICD implanted, 6 had a high-risk status for SCD, and the

Table 1  Clinical parameters of 446 mutation-carrying relatives at first cardiological evaluation

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>All mutation carriers (n = 446)</th>
<th>Mutation carriers with clinical HCM (n = 107)</th>
<th>Mutation carriers without clinical HCM (n = 339)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.3 ± 17.6 (446)</td>
<td>45.4 ± 17.8 (107)</td>
<td>37.4 ± 17.1 (339)**</td>
</tr>
<tr>
<td>Aged &lt;40 years</td>
<td>235 (446, 52.7%)</td>
<td>42 (107, 39.3%)</td>
<td>193 (339, 56.9%)**</td>
</tr>
<tr>
<td>Aged 40–65 years</td>
<td>181 (446, 40.6%)</td>
<td>50 (107, 46.7%)</td>
<td>131 (339, 38.6%)</td>
</tr>
<tr>
<td>Aged &gt;65 years</td>
<td>30 (446, 6.7%)</td>
<td>15 (107, 14.0%)</td>
<td>15 (339, 4.4%)</td>
</tr>
<tr>
<td>Male</td>
<td>195 (446, 43.6%)</td>
<td>61 (107, 57.0%)</td>
<td>134 (339, 39.5%)**</td>
</tr>
<tr>
<td>Clinical diagnosis of HCM</td>
<td>107 (446, 23.9%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Palpitations</td>
<td>72 (444, 16.2%)</td>
<td>13 (105, 12.4%)</td>
<td>59 (339, 17.4%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>22 (446, 4.9%)</td>
<td>7 (107, 6.5%)</td>
<td>15 (339, 4.4%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (446, 1.6%)</td>
<td>2 (107, 1.9%)</td>
<td>5 (339, 1.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mutated gene</th>
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<th>Mutated gene</th>
<th>Mutated gene</th>
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<tbody>
<tr>
<td>MYBPC3</td>
<td>366 (446, 82.1%)</td>
<td>89 (107, 83.2%)</td>
<td>277 (339, 81.7%)</td>
</tr>
<tr>
<td>MYH7</td>
<td>38 (446, 8.5%)</td>
<td>12 (107, 11.2%)</td>
<td>26 (339, 7.7%)</td>
</tr>
<tr>
<td>TNNT2</td>
<td>20 (446, 4.5%)</td>
<td>3 (107, 2.8%)</td>
<td>17 (339, 5.0%)</td>
</tr>
<tr>
<td>TPM1</td>
<td>20 (446, 4.5%)</td>
<td>3 (107, 2.8%)</td>
<td>17 (339, 5.0%)</td>
</tr>
<tr>
<td>MYL2</td>
<td>2 (446, 0.4%)</td>
<td>0 (107, 0.0%)</td>
<td>2 (339, 0.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence of risk factors for SCD</th>
<th>Presence of risk factors for SCD</th>
<th>Presence of risk factors for SCD</th>
<th>Presence of risk factors for SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme left ventricular hypertrophy</td>
<td>4 (446, 0.9%)</td>
<td>4 (107, 3.7%)</td>
<td>0 (339, 0.0%)**</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>24 (318, 7.5%)</td>
<td>14 (82, 17.1%)</td>
<td>10 (236, 4.2%)**</td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>10 (231, 4.3%)</td>
<td>5 (53, 9.4%)</td>
<td>5 (178, 2.8%)</td>
</tr>
<tr>
<td>≥50 years</td>
<td>14 (87, 16.1%)</td>
<td>9 (29, 31.0%)</td>
<td>5 (58, 8.6%)**</td>
</tr>
<tr>
<td>Abnormal blood pressure response</td>
<td>44 (296, 14.8%)</td>
<td>13 (76, 17.1%)</td>
<td>31 (220, 14.1%)</td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>32 (215, 14.8%)</td>
<td>9 (49, 18.4%)</td>
<td>23 (166, 13.9%)</td>
</tr>
<tr>
<td>≥50 years</td>
<td>12 (81, 14.8%)</td>
<td>4 (27, 14.8%)</td>
<td>8 (54, 14.8%)</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>19 (446, 4.3%)</td>
<td>3 (107, 2.8%)</td>
<td>16 (339, 4.7%)</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>73 (446, 16.3%)</td>
<td>10 (107, 9.3%)</td>
<td>63 (339, 18.6%)</td>
</tr>
<tr>
<td>Previous cardiac arrest or VT</td>
<td>1* (446, 0.2%)</td>
<td>1 (107, 0.9%)</td>
<td>0 (339, 0.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative number of risk factors for SCD</th>
<th>Cumulative number of risk factors for SCD</th>
<th>Cumulative number of risk factors for SCD</th>
<th>Cumulative number of risk factors for SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 risk factors</td>
<td>298 (446, 66.8%)</td>
<td>70 (107, 65.4%)</td>
<td>228 (339, 67.3%)</td>
</tr>
<tr>
<td>1 risk factors</td>
<td>130 (446, 29.1%)</td>
<td>28 (107, 26.2%)</td>
<td>102 (339, 30.1%)</td>
</tr>
<tr>
<td>≥2 risk factors</td>
<td>18 (446, 4.0%)</td>
<td>9 (107, 8.4%)</td>
<td>9 (339, 2.7%)</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number and proportion (%).

HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; VT, ventricular tachycardia.
*Woman with manifest HCM at first cardiological evaluation at age 79, who developed ventricular fibrillation in the setting of a myocardial infarction at age 55 (at that time no manifest HCM).
Significant differences between carriers with and without a clinical diagnosis of HCM:*P-value < 0.05, **P-value < 0.01, *** P-value < 0.001.

(P-value = 0.011) and more carriers were evaluated for all risk factors (61% at first evaluation and 75% at last evaluation, P-value < 0.001). The cumulative number of risk factors also increased, but this increase in risk factors was not significant. Eventually, 25 of these 238 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 \textit{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 definition (n = 5), had extreme left ventricular hypertrophy (n = 1), and had manifest HCM and SCD in close relatives but insufficient to meet our definition of a positive family history for SCD (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 = 0.004) 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 0.26% per person-year). Two died of non-cardiovascular causes and two died unexpectedly (SCD rate of 0.13% per person-year).
A female carrier died at the age of 80 years with documented ventricular fibrillation. 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 in 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 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. None of the 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 (2.4% per person-year).

Since manifest disease could have been present long before the first cardiological evaluation, we also assessed disease penetrance and incidence in the 163 carriers who had no clinical diagnosis at first cardiological evaluation and received at least one further cardiological evaluation (Figures 4 and 5). The percentage of carriers diagnosed with HCM per patient-year was lower than 10% in carriers aged <40 years and higher than 10% in the older carriers (Figure 5). Of the 163 carriers in Figure 5, only 11 carriers were <15 years of whom only one (a female) developed hypertrophy.

### 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. Penetration of manifest HCM is known to be age-dependent and HCM is detected more often in males. This is also shown by our data because older age and male gender were 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. Disease penetrance in our study was lower than previously described, probably because affected relatives and probands were excluded. However, it shows that disease can still become manifest at old age and cardiological evaluations should continue until advanced age.
Figure 1 Flow chart showing outcomes on a clinical diagnosis of hypertrophic cardiomyopathy and risk factors for sudden cardiac death at first and last cardiological evaluation. HCM+, clinical diagnosis of hypertrophic cardiomyopathy; HCM−, no clinical diagnosis of hypertrophic cardiomyopathy; RF0, zero risk factors for sudden cardiac death (SCD); RF1, one risk factor for sudden cardiac death; RF ≥ 2, two or more risk factors for sudden cardiac death; F-U, follow-up.

Figure 2 Clinical diagnosis of hypertrophic cardiomyopathy and high-risk status for sudden cardiac death (manifest hypertrophic cardiomyopathy and ≥2 risk factors) during follow-up.
Risk factors for SCD were frequently present in predictively tested carriers both with and without manifest disease. A majority (53%) of carriers was evaluated cardiologically 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.\(^{20}\) 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 the 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 whether these risk factors are also associated with SCD in carriers without manifest disease, although SCD has been described in this group.\(^{21}\) 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 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 annual evaluation including risk stratification for SCD in all carriers. As SCD occurred only twice, both times in carriers with manifest HCM, our study suggests that risk stratification for SCD may be omitted as long as HCM is not yet manifest. Our results on disease penetrance and incidence provide more insight in the optimal frequency of cardiological evaluations. The incidence of a clinical diagnosis of HCM during follow-up after the first cardiological evaluation differs with age, with less carriers per year developing HCM under the age of 40 years (Figure 5). It is unlikely that this is due to the screening interval, since this is not different in carriers of different ages. Our data suggest that in carriers <40 years without hypertrophy at first evaluation hypertrophy develops more slowly, although the small number of carriers <15 years of age allows no definite conclusions for this age group. Therefore, the frequency of cardiological evaluations in mutation carriers between 15 and 40 years without manifest disease can possibly be decreased to, for example, once every 2 years. 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 \(\text{MYBPC3}^{\text{\textregistered}}\) gene due to the presence of three frequent Dutch founder mutations in the \(\text{MYBPC3}^{\text{\textregistered}}\) gene.\(^{22,23}\) 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 generalized to predictively tested carriers of a mutation in other sarcomeric genes. Mutations in the \(\text{MYBPC3}^{\text{\textregistered}}\) gene, however, are worldwide one of the most frequent causes of HCM, accounting for \(\sim 30\%\) of all identified HCM mutations.\(^{7,24–27}\)

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.\(^{5,16,29}\) not to mention the practice in asymptomatic HCM mutation carriers. 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.

Since 24% of the carriers already had a clinical diagnosis of HCM at the time of the first cardiological evaluation and DNA diagnosis, the HCM diagnosis-free survival times estimated in the present sample are biased upwards. Due to the presence of asymptomatic HCM, more precise estimates can be only be obtained by regular screening of mutation carriers that were HCM free at the first evaluation, preferably starting at a young age to prevent bias due to selection.

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.
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, possibly allowing less frequent cardiological evaluations (for example once every 2 years instead of annually) in carriers between 15 and 40 years 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 predictively tested 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 predictively tested mutation-carrying relatives is lower than in probands, and that the ACC/AHA recommendations need revision to accommodate for mutation-carrying relatives, i.e. the recommended screening policy appears unnecessary intensive and frequent. More recent guidelines already have adapted the screening frequency in mutation carriers without manifest disease; however, they still advise intensive screening including risk stratification for SCD.10,31

Prolonged follow-up is needed to (i) evaluate the prognostic impact of risk factors for SCD, and (ii) to determine the optimal screening policy (risk stratification, screening interval) in asymptomatic mutation-carrying relatives with a wide spectrum of gene mutations. Including probands and affected relatives could also provide more insight in the natural history of HCM.

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References


