Hypertrophic cardiomyopathy: towards an optimal strategy
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Introduction and outline of this thesis

1.2 Scope and outline of this thesis
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More and more HCM mutation carriers have been identified by means of predictive DNA testing in the last decade and it is expected that their number will continue to rise. Until today cardiological care for these so called ‘asymptomatic’ -they have no symptoms or not enough symptoms to consult a doctor, but more importantly they are not known to have manifest HCM before DNA-testing- mutation carriers is based on assumptions and expert opinions only and is not evidence based. The current consensus document, dating from 2003, advices yearly cardiological evaluation including risk stratification for SCD. Following this guideline would pose an enormous and increasing demand on health care and could also be burdensome for the mutation carriers. This advice, however, is created with the knowledge gained from studies on patients with manifest HCM. It is known that sudden cardiac death can occur in patients with manifest disease with little or no symptoms of their disease. Risk stratification in patients with manifest disease can identify patients at high risk and in them SCD can be prevented by ICD implantation. It is to be expected that this kind of risk stratification in ‘asymptomatic’ mutation carriers who are found to have manifest disease after DNA-testing is also effective. There are as yet no studies on risk factors for SCD in ‘asymptomatic’ mutation carriers, especially not in mutation carriers without manifest disease.

With the number of ‘asymptomatic’ mutation carriers increasing and cardiologists more frequently reporting the absence of manifest disease, we wondered whether following the guideline and regularly performing extensive cardiological evaluations in all of these carriers was beneficial for them. Perhaps, we could identify a subgroup of mutation carriers who had a low risk of SCD and in whom cardiological evaluation was unnecessary or could be less extensive or less frequent or in whom DNA testing was unnecessary. To answer this question a study was designed called ESCAPE-HCM, Evaluation of Screening of Asymptomatic PatiEnts with Hypertrophic CardioMyopathy. In chapter 2.1 the design of this study is presented. In chapter 2.2 the follow-up results of the ESCAPE-HCM study are shown, in particular how many mutation carriers developed a high risk status, if SCD occurred and if prognostic evaluation of risk factors for SCD was possible. In chapter 2.3 the present consensus document on cardiological care is compared on cost effectiveness with the cardiological care that is suggested by the results of the ESCAPE-HCM study.

Main outcome measures in the ESCAPE-HCM study are SCD and risk factors for SCD. Although the current guidelines direct in the use of six major risk factors in risk stratification for SCD in HCM patients and mutation carriers, studies on these risk factors sometimes reported conflicting data and a systematic overview of studies had never been published. Although such an overview would report on studies with a population of patients with manifest HCM of whom mutation status was unknown, we thought it still would be valuable for future guidelines on HCM and could also guide us in which other possible risk factors had to be studied in our population of mutation carriers. Our systematic review of established and possible risk factors for SCD is presented in chapter 3.1.

In chapter 3.2 we report the prevalence of manifest HCM and of the six major risk factors in our asymptomatic carriers of a MYBPC3 gene mutation at the first cardiological evaluation after predictive DNA testing. Risk factors for SCD were present in carriers with and without HCM. Since risk stratification was incomplete in a considerable proportion of mutation carriers, we wondered if this care was given conform international guidelines. In chapter 3.3 we evaluated Dutch cardiologists’ knowledge of and adherence to international guidelines on risk stratification and prevention of SCD in mutation carriers with and without manifest HCM.
SCD is almost exclusively described in patients with manifest disease. In **chapter 3.4**, however, we present two cases of asymptomatic individuals who were resuscitated from ventricular fibrillation who developed manifest and genetically confirmed HCM only years after their event, showing that relatives without manifest disease might be at risk for SCD.

Although risk stratification focuses on clinical risk factors, genetic modifiers can probably also influence the phenotypic expression, like the presence of left ventricular hypertrophy and risk of SCD. In **chapter 3.5** we assess a possible association of genetic polymorphisms in the rennin-angiotensin-aldosteron system and left ventricular hypertrophy in HCM mutation carriers.

With the ESCAPE-HCM study designed to answer a single very important question other research questions arose. Our patient population consisted of relatives who were found to be mutation carriers after predictive DNA testing. It was unknown how many of the relatives at risk (first degree relatives of the proband and second degree relatives in case the connecting first degree relative had died) who were eligible for DNA testing, really attended our cardiogenetics outpatient clinic for genetic counselling and DNA testing. This so called uptake of genetic counselling and of DNA testing is presented in **chapter 4.1**.

In the ESCAPE-HCM study all mutation carriers received the cardiological care as advised by the guidelines. This consists of regular extensive cardiological evaluations with an echocardiogram, Holter recording and exercise test. These evaluations can be quite burdensome especially when one is still ‘asymptomatic’. We therefore wanted to know what the quality of life and the levels of psychological distress were in these mutation carriers compared to the general population and what their opinion was on the genetic counselling and cardiological care. This could also serve as a baseline measurement in case the ESCAPE-HCM study results would suggest interventions in cardiological care, like less frequent cardiological evaluations. In **chapter 4.2** the quality of life and psychological distress of mutation carriers (both probands and mutation carrying relatives) are compared to normative data of the general Dutch population and possible predictors of quality of life and psychological distress are evaluated. In **chapter 4.3** we evaluated the opinions of predictively tested mutation carriers on received genetic counselling and testing, and cardiological care. One of the main disadvantages of predictive DNA testing in hereditary diseases is that disclosure of DNA test results may have social implications such as low access to insurance. In **chapter 4.4** we assess frequency and type of problems encountered by HCM mutation carriers applying for insurance, and associations with carriers’ characteristics.

The results of our research may have several implications for the management of cardiogenetic care. These implications are discussed in **chapter 5** (general discussion).