# “Sudden Death-Genetic Risk” Living with the risk of serious arrhythmias and sudden cardiac death

*-A prospective multicenter-study on patient-reported outcomes in individuals with familial Long QT syndrome and Hypertrophic cardiomyopathy who received genetic investigation and counseling in Norway, 2005-2007.*

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## Scientific environment

This work was carried out at the Centre of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Department of Pathology and Medical Genetics, St. Olavs Hospital HF, and the Department of Public health and General Practice, Norwegian University of Science and Technology (NTNU). The project was funded by the Western Norway Regional Health Authority and the Faculty of Medicine and the Genetic Epidemiology Research Group, University of Bergen (UIB). The PHD-candidate was granted admission at the Faculty of Medicine (UIB) and has followed doctoral training and PhD-courses at UIB and NTNU.

Professor Nina Øyen from Centre of Medical Genetics and Molecular Medicine, Haukeland University Hospital and the Genetic Epidemiology Research Group, UIB has been the principal advisor. Co-advisors have been Professor and Deputy Rector of the UIB, Berit Rokne, and Professor Karin Nordin, both from the Department of Public Health and Primary Health Care.

Further, there was scientific collaboration during parts of the study with Cathrine Bjorvatn, Gunilla Bergstrøm, Gottfried Greve, Trond Leren, Knut Erik Berge, Geir Egil Eide, Gerd Kvale, and Lars Fredrik Engebretsen.

Geir Egil Eide og Cathrine Bjorvatn is also co-authors of various papers in the study.

The Phd fellow is employed as genetic counselor and researcher at Department of Pathology and Medical Genetics, St. Olavs Hospital HF.

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# 1. Abstract

**Background:** Patients with a clinical diagnosis or a family history of the two distinct entities Long QT syndrome (LQTS) and Hypertrophic cardiomyopathy (HCM) have a higher genetically based risk of serious arrhythmias and sudden cardiac death (SCD) than the general population. Living with this health threat may affect health status and cause anxiety. The scientific development in the field of genetics has made it possible to offer these patients genetic investigation. However, in what way, this health threat affects the patients receiving genetic investigation and counseling is unknown. Patient- reported outcome measures may provide better understanding of these individuals' situation, which is essential for the further development of improving quality of care in cardio-genetic counseling.

**Aims:** The overall aim of this study was therefore to obtain more knowledge about the health status, levels of general anxiety and depression, and symptoms of heart-focused anxiety in individuals receiving genetic investigation and counseling because of familial LQTS or familial HCM. The specific aims were;

**I)** To investigate health status; in comparison to expected scores of Norwegian general population, and in relation to socio-demographic variables and clinical status;

**II)** To investigate general anxiety, depression, and physical health, in comparison to expected scores of Norwegian general population or norm scores, in patients with familial LQTS as compared to patients with familial HCM, and in relation to the role of three distinct symptoms of heart-focused anxiety (avoidance, attention, and fear);

and **III)** To explore if factors such as a family history of sudden cardiac death, patient knowing whether other relatives' previously had undergone genetic testing, perceived general health, self-efficacy expectations, and satisfaction with genetic counseling (affective, instrumental, procedural) predict heart-focused anxiety up to one year after the genetic counseling.

**Methods:** In a prospective multi-site study at three university hospitals in Norway during 2005-2007, all patients referred for medical genetic investigation and counseling because of familial LQTS or familial HCM, over 17 years of age, and not previously genetically tested, were eligible to participate. Patients referred were family members and other appropriate relatives subsequently following the identification of a LQTS or HCM- causative mutation in an index case or individuals in whom a cardiologist had established or suspected a clinical diagnosis of LQTS or HCM. Among 175 patients asked, 127 (126) patients completed a questionnaire before the counseling session, and were asked to fill in questionnaires at several time points after the counseling session (right after, 4 weeks, 6 months, and 1 year after). The patient-reported outcomes were based on The SF-36 Health Survey, Hospital Anxiety and Depression Scale, Cardiac Anxiety Questionnaire, Bergen Genetic Counseling Self-efficacy Scale, Satisfaction with Genetic counseling, socio-demographic and clinical variables. *Descriptive, comparative and prospective analyses* were performed. Expected scores of Norwegian general population were calculated for health status, general anxiety and depression, for baseline comparisons. *Multiple linear analyses* were used to evaluate the relationship of socio-demographic, clinical variables and health status. *Hierarchical regression analyses* were used to

assess the ability of three distinct symptoms of heart-focused anxiety (avoidance, attention, and fear) to predict levels of general anxiety, depression, and physical health. *Mixed linear modelling (MLM)* was used to investigate predictors and changes over time of the subscales of Cardiac Anxiety Questionnaire (CAQ); avoidance, attention, and fear. All predictors were entered into MLMs to assess both their main effects and their possible interaction with time.

**Results: I)** Among the 127 study participants, 88 patients (69.3 %) were referred for familial LQTS, whereas 39 patients (30.7 %) were referred for familial HCM. Ninety-five patients (74.8 %) were family members and other appropriate relatives at genetic risk of LQTS or HCM, whereas individuals in whom a cardiologist had established a clinical diagnosis, 12 patients (9.4 %) were affected with LQTS and 20 patients (15.7 %) were affected with HCM. Fifty-seven patients (44.9%) reported to have experienced a sudden cardiac death in a family member. Overall, patients reported significant poorer general health as compared to expected scores of the general population. Better health status scores were related to patients' employment, higher education level, and referral to genetic counseling by a relative. Patients with a clinical diagnosis of HCM had markedly reduced health status as of compared to the general population, as compared to the patients at genetic risk of LQTS or HCM, and also compared to patients with a clinical diagnosis of LQTS. **II)** Overall, the patients reported significant higher levels of general anxiety as compared to expected scores. Patients at genetic risk for LQTS or HCM scored better on physical health as compared to expected scores, whereas the patients with a clinical diagnosis of LQTS or HCM showed poorer physical health as compared to expected scores. Compared to

the patients that were referred for familial LQTS, patients referred for familial HCM had poorer physical health and higher scores of heart-focused anxiety. Two distinct symptoms of heart-focused anxiety (avoidance and fear) were independently related to levels of general anxiety and depression, as well as to physical health (beyond the effect of gender, age, clinical diagnosis, and family history with a recent sudden cardiac death. **III)** A family history of sudden cardiac death in close relatives, uncertainty whether other relatives had genetic testing, poorer perceived health, low self-efficacy expectations before genetic counseling, and low procedural satisfaction immediately after the genetic counseling predicted higher levels of heart-focused anxiety up to one year after the counseling session (beyond the effect of questionnaire time points, age, gender, clinical diagnosis, and genetic test result). A mutation positive result predicted higher scores of cardio-protective avoidance 6 months after genetic counseling.

**Conclusions:** Patients living with the health threat of serious arrhythmias and sudden cardiac death because of familial LQTS or familial HCM perceive their health to be poorer and have a higher general anxiety level compared to expected scores in the general population, before receiving genetic counseling. Distinct symptoms of heart-focused anxiety such as the extent to which these individuals report cardio-protective avoidance and fear about heart sensations seem to influence their reporting of general anxiety, depression, and physical health. Predisposed individuals for heart-focused anxiety were patients who had experienced a close relative's sudden cardiac death and patients uncertain whether other relatives previously had undergone genetic testing. However, satisfaction with the procedural parts of genetic counseling was

predictive of decreased levels of heart-focused anxiety. The resources of greatest prognostic importance to prevent heart-focused anxiety may be the way individuals perceive their general health and their self-efficacy expectations. The present findings indicate that individuals undergoing genetic investigation and counseling for familial LQTS or familial HCM are vulnerable in both health-related and psychological domains before genetic counseling, and may benefit from a closer collaboration between the genetic counselor and the cardiologist addressing their experience of cardiac symptoms to a greater extent.

# List of papers

**Paper I**

Hamang, A., Eide, G.E., Nordin, K., Rokne, B., Bjorvatn, C., & Øyen, N. (2010). Health status in patients at risk of inherited arrhythmias and sudden unexpected death compared to the general population. *BMC Medical Genetics* 11:27

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**Paper II**

Hamang A, Eide GE, Nordin K, Rokne B, Øyen N. (2011). General anxiety, depression, and physical health in relation to symptoms of heart-focused anxiety among patient living with the risk of serious arrhythmias and sudden cardiac death. *Health and Quality of Life Outcomes*, Under 2nd review

**Paper III**

Hamang A, Eide GE, Nordin K, Rokne B, Bjorvatn C, Øyen N. (2011). Predictors of heart-focused anxiety in patients undergoing genetic investigation and counseling of Long QT syndrome or Hypertrophic cardiomyopathy: A one year follow-up. *Journal of Genetic Counseling*

*http://www.springerlink.com/content/y6u81618328378t2/fulltext.pdf*

DOI 10.1007/s10897-011-9393-6

# List of abbreviations

| | |
|---|---|
| ACC | American College of Cardiology |
| AHA | American Heart Association Task Force |
| ANOVA | Analysis of variance |
| BGCSES | The Bergen Genetic Counseling Self-efficacy Scale |
| CAQ | The Cardiac Anxiety Questionnaire |
| ESC | European Society of Cardiology |
| β-blockers | Beta blocker medication |
| DSM-IV | The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association |
| ECG | Electrocardiogram |
| HADS | Hospital Anxiety and Depression scale |
| HCM | Hypertrophic cardiomyopathy |
| HUNT | The Nord-Trøndelag Health Study |
| ICD | Intracardial defibrillator |
| ICD-10 | International Classification of Diseases-10 |
| IQOLA | The International Quality of Life Assessment Project |

| | |
|---|---|
| LQTS | Long QT syndrome |
| LQT 1-3 | Long QT phenotypes 1 to 3 |
| MLM | Mixed linear modeling |
| OMIM | Online Mendelian Inheritance in Man |
| PROM | Patient-reported outcome measures |
| SF-36 | Short Form 36 |
| TdP | Torsade-de Pontes |
| WHO | The World Health Organization |

# Glossary

**Autosomal Dominant**: The situation in which the disease can be expressed even when only one chromosome harbours the mutation.

**Autosomal Recessive**: The situation in which the disease can be expressed only when both chromosomes of a pair are abnormal.

**Cascade Testing**: Procedure whereby all first-degree relatives of a genotype-positive index case are tested in concentric circles of relatedness. If one of the family members is genotype positive, all his/hers first-degree relatives should be tested continuing this process following each genotype-positive family member.

**Disease-causing Mutation**: A DNA sequence variation that represents an abnormal allele and is not found in the normal healthy population but exists only in the disease population and produces a functionally abnormal product.

**Expressivity**: The level of expression of the phenotype, and when the manifestations of the phenotype in individuals who have the same genotype are diverse, the phenotype is said to exhibit variable expressivity.

**First-Degree Relative**: A blood relative who is a person's parent, sibling, or child.

**Founder Mutation**: The occurrence of a particular gene mutation at increased frequencies within a given population due to its presence in a small isolated group of ancestors that directly gave rise to the current population.

**Genotype**: A person's genetic or DNA sequence composition at a particular location in the genome.

**Index Case/Proband**: The person or patient who first draws clinical attention to a particular family in a genetic or epidemiologic investigation.

**Mutation**: A change of the DNA sequence within the genome.

**Mutation- Disease Causing**: A DNA sequence variation that represents an abnormal allele and is not found in the normal healthy population and produces a functionally abnormal product.

**Penetrance**: The likelihood that a gene mutation will have any expression at all. In the situation in which the frequency of phenotypic expression is less than 100 %, the genetic defect is said to be associated with reduced or incomplete penetrance.

**Phenocopy**: An individual who manifests the same phenotype (trait) as other individuals of a particular genotype but does not possess this genotype himself/herself.

**Phenotype**: A person's observed clinical expression in terms of a morphological, biochemical, or molecular trait.

**Variants of Uncertain Significance (VUS)**: A mutation or genetic variation with uncertain clinical significance.

# List of appendices

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Appendix 3: REK recommendation

Appendix 4: Act of Biotechnology (relevant chapters)

# 1. Introduction

International guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (ACC/AHA/ESC 2006) emphasize the importance of genetic testing in Long QT syndrome (LQTS) families and the usefulness of testing in families with Hypertrophic cardiomyopathy (HCM) (Zipes et al, 2006). LQTS is a channelopathy (Kramer & Zimetbaum, 2011) and HCM is a sarcomere disorder (Watkins, et al., 2011). Common for the patients with familial LQTS and familial HCM is a genetically based increased risk for serious arrhythmias. Both patients with a clinical diagnosis, as well as their relatives who are at genetic risk of developing the disease, therefore live with the threat of a premature sudden cardiac death (Maron, 2003; Maron, 2009; Vincent, 2005). Living with such a health threat may have big consequences for the health and wellbeing of these individuals.

In health sciences the concepts of health status, general anxiety and depression, and heart-focused anxiety are often researched. These concepts may also be particularly relevant to study in individuals who receive genetic investigation and counseling because of familial LQTS or familial HCM. Firstly, the clinical diagnosis of LQTS or the clinical diagnosis of HCM may by themselves give considerable discomfort, when patients experience syncope, palpitations, or other debilitating symptoms. In addition, emotional reactions are likely, since the risks of cardiac symptoms are so immediate and possibly fatal. Secondly, LQTS and HCM are autosomal dominant disorders, which mean children, siblings and parents of a mutation carrier have a 50 percent risk of also being affected, thus they are also living with risk of serious cardiac symptoms. The penetrance (likelihood for actually developing the disease) is however varying, which leads to uncertainty of ever experiencing clinical symptoms of the disorder. Thirdly, identifying individuals with a high risk implies medication and life-style advice to prevent sudden cardiac death. Since the penetrance is not 100%, no-one will ever know whether the medication which may have side-effects was necessary.

Moreover, relevant health advice implies that excessive physical activity should be avoided as well as prolonged ‘stress’. Lastly, individual differences may potentially influence on how patients adapt to living with familial cardiac disorders.

Patient perspective has become essential for quality of care. While the research concerning LQTS and HCM has focused on genes, mutations, morbidity and mortality, very little research has been based on patient-reported outcomes of adult persons undergoing the process of genetic investigation and counseling for familial LQTS or familial HCM. The impact of measuring patient-reported outcomes may pertain to provision of important understanding of patients physical or psychological vulnerabilities that otherwise might be overlooked. Further it may give information on disease progression, results of interventions, and establishing a more common understanding between the patient and the health-care provider (Valderas & Alonso, 2008).

The aim of genetic counseling is “helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease”. The rapidly developing gene technology has made it possible to identify individuals with an increased risk for familial disorders such as LQTS or HCM. This has resulted in increasing needs to develop health communications, counseling services, and interventions for helping patients to cope with genetic risk. Knowledge based on patients’ perspective is essential for the continuation of developing cardio-genetic counseling. Thus, the focus of this thesis will be from the patient perspective using patient-reported outcome measures that reflect health status, levels of general anxiety and depression, as well as symptoms of heart-focused anxiety. There will also be a focus on patients’ self-efficacy expectations and satisfaction with genetic counseling.

One thing is for certain, these concepts are close to the heart in more ways than one. Not only is it the physical side of a hearth that beats in a rhythm, but it is also all the emotional components we attach to it, and that also may affect the physical heart.

# 2. Familial long QT syndrome and familial hypertrophic cardiomyopathy

## 2.1 Long QT syndrome - a channelopathy

LQTS is a congenital disorder characterized by a prolongation of the QT interval on electrocardiogram (ECG) and an increased risk of ventricular arrhythmia e.g. Torsades-de Pointes (TdP), associated with increased risk for syncope, cardiac arrest, or sudden cardiac death, especially in young individuals (Vincent, 2005). The diagnosis is based on the measurement of the QT-interval in ECG, clinical history, and/or a family history of LQTS and sudden cardiac death (Schwartz, 2006; Crotti et al., 2008). Diagnostic criteria based on the characteristic features of LQTS are shown in table 2.1.

Molecular genetic investigation has become an important supplement in the diagnostics, after identification in the mid-nineties of the first three LQTS genes KCNQ1, KCNH2 and SCN5A associated with the most common phenotypes of LQT1, LQT2 and LQT3 (Wang et al., 1995; Curran et al., 1995; Wang et al., 1996). The type of LQTS influences clinical course, in that most cardiac events are triggered by exercise and stress in LQT1, by emotional stress such as auditory stimuli in LQT2, while most cardiac events happen under sleep or rest for LQT3 (Schwartz et al., 2001). The lethality of cardiac events is suspected to be in the range from 2 to 20 % (Zareba et al., 1998). LQTS may be inherited as an autosomal dominant trait with either full or reduced penetrance (Romano-Ward syndrome) (Ward, 1964; Romano, Gemme & Pongiglione, 1963; Romano, 1965), or as an autosomal recessive trait (Jervell-Lange-Nielsen syndrome with congenital deafness)(Schwartz et al., 2006; Jervell & Lange-Nielsen, 1957). Mutation carriers may have symptoms or have prolonged QT-interval in ECG, but carriers with neither symptoms nor prolonged QT-interval may also have

an increased risk for sudden cardiac death, making molecular testing essential for initiating medication (β-blockers) and life-style advice for asymptomatic mutation carriers. Reported prevalence varies from 1/10 000 to 1/2500 (Crotti et al., 2008). In some parts of the world it is estimated to be higher due to founder mutations which are also the case in Norway (Berge et al., 2008).

Table 2.1 Diagnostic criteria for Long QT syndrome (LQTS) according to EKG findings, clinical history, and family history

| | | | Points |
|---|---|---|---|
| ELECTROCARDIOGRAPHIC FINDINGS # | | | |
| A | QTc^ | > 480 ms | 3 |
| | | 460 – 470 ms | 2 |
| | | 450 – 459 (male) ms | 1 |
| B | Torsade de pointes * | | 2 |
| C | T wave alternans | | 1 |
| D | Notched t wave in 3 leads | | 1 |
| E | Low heart rate for age @ | | 0.5 |
| CLINICAL HISTORY | | | |
| A | Syncope * | With stress | 2 |
| | | Without stress | 1 |
| B | Congenital deafness | | 0.5 |
| FAMILY HISTORY $ | | | |
| A | Family members with definite LQTS | | 1 |
| B | Unexplained sudden cardiac death below age 30 among immediate family members | | 0.5 |

Source: Crotti et al. (2008). Congenital long QT syndrome. Orphanet Journal of Rare Diseases, 3:18. http://www.ojrd.com/content/3/1/18

# In the absence of medications or disorders known to affect these electrocardiographic features

^ QTc calculated by Bazett's formula where QTc = QT/√RR

* Mutually exclusive

@ Resting heart rate below the 2nd percentile for age

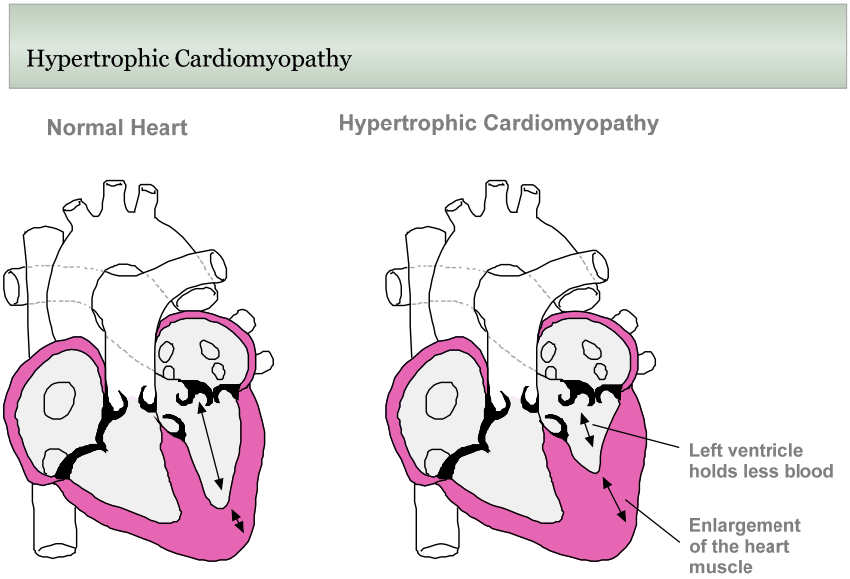
$ The same family member cannot be counted in A and B

SCORE: ≤ 1 point = low probability of LQTS, > 1 to 3 points = intermediate probability of LQTS, ≥ 3.5 points = high probability of LQTS

## 2.2 Hypertrophic cardiomyopathy - a sarcomere disease

HCM is an excessive thickening of the heart muscle in the left and/or right ventricle (Maron, 2002; Watkins et al., 2011) (Fig. 2.1), and it is defined by the presence of this increased ventricular wall thickness or mass, having ruled out hypertension and valve disease (Elliott et al., 2008).

Figure 2.1 Difference between a normal heart and hypertrophic cardiomyopathy.




Myocyte disarray and fibrosis is typical features (Maron, 2002; Watkins et al., 2011). The symptoms are dyspnea, palpitations, syncope/near syncope's, chest pains and arrhythmias. Like in LQTS, sudden cardiac death can present as first manifestation of the disorder (Maron, 2002). Diagnosis is made with 2-dimensional echocardiography, and the cardiac disorder may be suspected because of a heart murmur, abnormal ECG, symptoms and a positive family history (Maron, 2002). Molecular screening is available. The genetic traits are mainly autosomal dominant with varying penetrance, but also autosomal recessive, X-linked, and sporadic (5%). Established symptomatic

treatment exists, such as medications, pacemaker, intracardial defibrillator (ICD), surgery, and advice for daily living. HCM is the most prevalent inherited cardiac disorder, affecting 1/500. Overall, the annual mortality rate from HCM is estimated to be 1 to 5 % (Maron, 2002).

## 2.3 Common characteristics of Long QT syndrome and Hypertrophic cardiomyopathy

Although, LQTS is a channelopathy (Goldenberg & Moss, 2008) and HCM is a sarcomere disease (Watkins et al., 2011), genetic investigation and counseling follows the same protocol for both familial cardiac disorders. This is based on the two disorders many common characteristics in the genetic setting. In addition, both LQTS and HCM patients face a serious health threat, serious symptoms, the threat of sudden cardiac death, and the possibility that their children have inherited the same disorder. Both entities have incomplete penetrance and variable expression. There are great uncertainties regarding symptoms, management and prevention, and both cardiac disorders require adjustments of life style and avoidance of triggers. The complexities in managing these patients and their relatives at risk, calls for clinicians with considerable experience and knowledge of the disorders, and guidelines that reflect international expert opinion (Garratt et al., 2010).

## 2.4 International guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

International guidelines specifically address familial cardiac disorders such as LQTS and HCM with regards to management and the prevention of sudden cardiac death (Zipes et al., 2006). Sudden cardiac death (SCD) is according to the Task Force of Sudden Cardiac Death, European society of cardiology defined as “Natural, non

traumatic death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of symptoms. Pre-existing heart-disease may have been known to be present, but the time and mode of death are unexpected" (Priori et al., 2002). LQTS is responsible for a significant proportion of SCDs in young people without structural heart disease (Berul, 2008). In young people and in athletes the most common cause of death in the United States has been reported to be HCM (Maron, 2009; Maron, 2003). In Norway there is no available information at present of the incidence of sudden cardiac death due to familial LQTS or familial HCM. It is expected to be at least similar to international numbers.

The question if a sudden cardiac death or an episode of aborted cardiac arrest was caused by a familial disorder such as LQTS or HCM, and the consequences that other relatives may be at risk, are a concern that adds to the trauma for the families that experience this. According to the guidelines, lifestyle changes such as avoidance of competitive sports activity are recommended, for both LQTS and HCM patients. Beta blockade is recommended for patients with a prolonged QT interval and is part of the management of HCM. Implantation of ICD remains controversial however recommended for LQTS patients with previous cardiac arrests and HCM patients who have sustained ventricular tachycardy and /or ventricular fibrillation, receiving optimal medical therapy and have prospects of good functional status for over 1 year. The guidelines emphasize the importance of genetic testing in LQTS families and the usefulness of testing in families with HCM , thus genetic investigation and counseling is warranted in these families (Zipes et al., 2006).

# 3. Genetic investigation and counseling of familial Long QT syndrome and familial hypertrophic cardiomyopathy

## 3.1 Genetic investigation

Today, individuals with an increased risk of developing life-threatening arrhythmias because of LQTS or HCM can be identified with a genetic investigation. Expert Consensus Recommendations has been developed for the use and role of genetic testing for potentially heritable cardiac conditions (Ackerman et al., 2011). A summary of expert consensus recommendations for the state of genetic testing for both LQTS and HCM is shown in table 3.1.

The genetic investigations of familial LQTS or familial HCM comprise mainly two forms of genetic testing, diagnostic and predictive testing. Diagnostic testing involves confirming a suspected or evident clinical diagnosis in an index case, whereas predictive testing is used to determine whether a patient with a proven gene mutation in a close family member has the gene mutation that involves risk for future disease.

Mutations in genes encoding cardiac potassium or sodium ion channels can be found in two-thirds of patients affected with LQTS (Schwartz et al., 2001; Splawski et al., 2000; Zareba et al., 1998). An overview over molecular genetics of LQTS in the clinical setting is shown in table 3.2.

Predictive genetic testing is a valuable tool to identify at-risk individuals by “cascade testing” (genetic testing of a mutation carrier’s first degree relatives) in the families

that are affected with LQTS. This is especially important, because predictive genetic testing is the only way to rule out LQTS in such family members because of the variable penetrance and expression of the disorder. However, because diagnostic genetic testing identifies a disease causing mutation in approximately 75% to 80 % of clinically affected LQTS patients (Schwartz, 2006; Ackerman et al., 2011), a negative diagnostic genetic test cannot completely exclude the diagnosis of LQTS by itself. Rare variants of uncertain significance (VUS) in the LQT1-3 genes also complicate the interpretation of gene test results (Ackerman et al., 2011). Therefore, clinical diagnostic genetic testing should not be performed on index cases without cardiology consultation according to the recommendations (Ackerman et al., 2011).

Genetic investigation has also become available in families with HCM, where dominant mutations in sarcomeric protein genes are associated with a high risk of sudden cardiac death (Bos et al., 2009). The molecular genetics of HCM is shown in table 3.3. Mutations in 14 genes that encode different proteins of the cardiac sarcomere cause the autosomal dominant form of HCM. Two of the genes predominate; The MYBPC3 (myosin-binding protein C) and MYH7 (β-myosin heavy chain) (Bos et al., 2009). In HCM patients, mutations in one of those genes can be found in 30-80 % depending on case ascertainment (Andersen et al., 2009; Maron et al., 2007; Van Driest et al., 2005), thus more limitations apply as compared to LQTS diagnostic testing in excluding a HCM diagnosis. However diagnostic genetic testing is recommended for patients with a firm clinical diagnosis of HCM, first of all because it may benefit family members and other relatives. Furthermore, predictive genetic testing of patients with a proven gene mutation in a close family member is recommended over clinical screening because ECG or echocardiographic abnormalities may be absent or subtle, or develop at a later stage (Ackerman et al., 2011).

Table 3.1 Summary of Expert Consensus Recommendations*

**State of genetic testing for Long QT syndrome (LQTS)**

**Class I (is recommended)**

- Comprehensive or LQTS1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing (diagnostic) **is recommended** for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.
- Comprehensive or LQTS1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing (diagnostic) **is recommended** for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc> 480 ms (prepuberty) or > 500 ms (adults).
- Mutation-specific genetic testing (predictive) **is recommended** for family members and other appropriate relatives subsequently following the identification of a LQTS-causative mutation in an index case.

**Class II (may be considered)**

- Comprehensive or LQTS1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing (diagnostic) **may be considered** for any asymptomatic patient with otherwise idiopathic QTc values >460 ms (prepuberty) or > 480 ms (adults) on serial 12-lead ECGs.

**State of genetic testing for Hypertrophic cardiomyopathy***

**Class I (is recommended)**

- Comprehensive or targeted (MYBPC3, MYH7, TNNI3, TNNT2, TPM1) HCM genetic testing (diagnostic) **is recommended** for any patient in whom a cardiologist has established a clinical diagnosis of HCM based on examination of the patient's clinical history, family history, and electrocardiography/ echocardiography phenotype.
- Mutation-specific genetic testing (predictive) **is recommended** for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case.

* Source: Ackerman et al. (2011). HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace., 13,* 1077-1109.

Table 3.2. Molecular genetics of Long QT syndrome (LQTS)*†

| Locus Name | Gene Symbol | Chromosomal Locus | Protein Name | % of LQTS attributed to mutations in this gene |
|---|---|---|---|---|
| LQT1 | KCNQ1 | 11p15.5 | Potassium voltage-gated channel subfamily KQT member 1 | 58% |
| LQT2 | KCNH2 | 7q35-q36 | Potassium voltage-gated channel subfamily H member 2 | 35% |
| LQT3 | SCN5A | 3p21 | Sodium channel protein type 5 subunit alpha | 5% |
| LQT5 | KCNE1 | 21q22.1-q22.2 | Potassium voltage-gated channel subfamily E member 1 | 1% |
| LQT6 | KCNE2 | 21q22.1 | Potassium voltage-gated channel subfamily E member 2 | 1% |

* http://www.ncbi.nlm.nih.gov/books/NBK1129/ accessed 6 June 2011, updated 20 October 2011, publisher; National Center for Biotechnology information (NCB1)

Table 3.3 Molecular genetics of Hypertrophic cardiomyopathy (HCM)*†

| Locus Name | Gene Symbol | Chromosomal Locus | Protein Name | % of HCM attributed to mutations in this gene |
|---|---|---|---|---|
| CMH1 | MYH7 | 14q12 | Potassium voltage-gated channel subfamily H member 2 | 35% |
| CMH4 | MYBPC3 | 11p11.2 | Myosin-binding protein C, cardiac-type | 40% |
| CMH2 | TNNT2 | 1q32 | Troponin T, cardiac muscle | 5% |
| CMH7 | TNNI3 | 19q13.4 | Troponin I, cardiac muscle | 5% |
| CMH3 | TPM1 | 15q22.1 | Tropomyosin 1 alpha chain | 2% |
| CMH10 | MYL2 | 12q23-q24.3 | Myosin regulatory light chain 2, ventricular/cardiac muscle isoform | Unknown |
| CMH8 | MYL3 | 3p | Myosin light polypeptide 3 | 1% |
| | ACTC1 | 15q14 | Actin, alpha cardiac muscle | Unknown |
| | CSRP3 | 11p15.1 | Cysteine and glycine-rich protein 3, muscle LIM protein | Unknown |
| CMH9 | TTN | 2q31 | Titin | |
| | ACTN2 | 1q42-q43 | Alpha-actinin-2 | Unknown |
| TNNC1 | | 3p21.3-p14.3 | | |

* http://www.ncbi.nlm.nih.gov/books/NBK1768/ accessed 6 July 2011, updated 20 October, publisher; National Center for Biotechnology information (NCB1)

## 3.2 Genetic counseling

The new possibilities we have today through technology and in dealing with familial cardiac disorders are reflected in the definition of genetic counseling from the National Society of Genetic Counselors (NSGC)(Resta et al., 2006).

> "Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates:
>
> - Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
> - Education about inheritance, testing, management, prevention, resources and research.
> - Counseling to promote informed choices and adaptation to the risk or condition"

The definition emphasize genetic counseling as a specialist field with the goal of communicating inherited risk information that is based on genetic investigation (Demarco et al., 2004), in a manner that can help the individual to adaptive coping processes. The practice and procedure of genetic investigation as well as the counseling to patients with familial LQTS or familial HCM is still under development, in order to be able to reach this important goal.

## 3.3 Current practice of genetic investigation, counseling and the Norwegian legislation

In Norway, the Act relating to the application of biotechnology in human medicine (Biotechnology act of 1994, and later Act of 2003, see Appendix) regulates clinical genetic activities first of all by paragraph 5-2 that states that "Genetic testing shall only be carried out for medical purposes if it has a diagnostic or therapeutic objective" (2003).

There has been a long tradition for genetic counseling that started already several decades before the first Biotechnology Act, however the current practice of genetic investigations in families with LQTS have only existed since approximately 2001 (Hamang et al., 2009), whereas HCM genetic investigations started approximately in 2004. The molecular genetic testing has been performed at Rikshospitalet in Oslo (Haugaa et al., 2005), whereas the genetic counseling has been conducted at the main regional tertiary hospitals throughout the country.

Today, the genetic investigation and counseling is mainly performed by a team of medical geneticists and genetic counselors. However, cardiologists also increasingly conduct diagnostic genetic testing as part of their clinical investigation in determining a patient's diagnosis. Collaboration between the heart departments and the specialized cardio-genetic clinics is essential because of the importance of establishing firm clinical diagnoses of index-cases (Ackerman et al., 2011).

In contrast to diagnostic genetic testing that can be performed without prior genetic counseling, the current Act regulates predictive genetic testing more strictly. In addition to the demand for a diagnostic or therapeutic objective for carrying out

testing, the law state that genetic counseling shall be given before, during, and after predictive genetic testing of the person. In cases where a child under 16 years is predictively tested, the child's parents, or other person who has parental responsibility should receive genetic counseling. Furthermore, written consent must be obtained of the counselees. And finally, "unless the test can detect a condition for which treatment may prevent or reduce damage to a child's health", testing children under 16 years of age is prohibited. However, since both LQTS and HCM can affect children and dangerous symptoms can be prevented, current practice performs predictive genetic testing on children.

## 3.4 Procedure of the genetic counseling sessions

Before the genetic counseling session the patient information and family history is verified in medical records, autopsy reports, and other relevant documents which are collected after approval of the patient and relatives involved. Apart from verifying diagnosis in medical records/autopsy reports etc, important parts of the genetic investigation are collecting information pertaining to previous genetic testing, incidence of the disease in the family, onset of disease in relatives with relevant diagnosis/symptoms, and exploring circumstances around sudden cardiac deaths in the family.

Typically the genetic counseling is offered over the course of two-three sessions. After a medical genetic review of the family history and available information, one pre-test session is offered to provide the patient and family with information (see table 3.4) and one disclosure session where the genetic test result is disclosed to the patient. Subjects discussed in the pre-test session, include prevalence, symptoms, clinical findings, prognosis, recurrence risk, genes, mutations, and treatment, as well as questions regarding genetic testing. Evaluation of the genetic risk is based upon family history, symptoms, clinical findings, and age of onset. Information from a genetic test is only a

supplement to the risk assessment today, since in many families, it is currently impossible to detect a gene mutation (see above). However once a gene mutation is identified in a patient, genetic testing of other relatives is possible.

In the genetic counseling session the genetic counselor aims to individualize the information based on the patient's need of information and support. Identification of a disease causing mutation may have implications for issues such as profession, education, driver license and insurance. Therefore, it may be relevant to discuss these matters as well.

Apart from that the patient is informed of the genetic test result and its implications in the disclosure session, important information from the pre-test session is repeated. In addition, the identification of other at-risk relatives is conducted together with the patient.

Patients that are proven mutation carriers and patients with inconclusive results are offered subsequent consultations and are referred for cardiac investigations, controls and follow up, whereas patients that have tested negative for the specific family mutation has no need for further cardiological follow up, from a medical standpoint.

The literature raises a number of ethical questions and emphasizes psychological issues that one should be aware of with regard to genetic testing and management of patients at risk of familial cardiac disorders (Aatre & Day, 2011; Charron et al., 2002; Mularczyk et al.,; van Langen et al., 2004). However, this literature has mainly been based on information from the clinician's perspective, and more specific knowledge about the patients' is needed.  Apart from that these patients face the risk of life

threatening events and are subjected to genetic testing, they may also experience symptoms, disability and reduced wellbeing as a result of living with familial LQTS or HCM. Patient perspectives of their health have not only become important in health research, but essential knowledge to achieving high quality care (Black & Jenkinson, 2009). This is further outlined below.

Table 3.4 Subject to be covered according to protocol for pre-test genetic counseling session of patients with familial LQTS or familial HCM

- Review of personal and family medical history (symptoms, clinical diagnosis, known heart-disorders in the family, anyone who died suddenly)
- Identification of a possible genetic risk (family history of a certain cardiac disorder or identification of a definite disease-causing mutation in an index case)
- Explanation about the nature of the familial disorder (incidence, age at onset, symptoms)
- Explanation of possible inheritance patterns (autosomal dominant/recessive)
- Review of appropriate testing options and its consequences (what does a test result mean, and implications of disclosure of test result.)
- Discussion of prevention strategies and disease management (prophylactic treatment, avoidance of triggers)
- Provision of genetic-related information and suggestion of reliable resources (patient information, online patients websites)
- Counseling to promote informed choices and adaptation to the risk or the disease
- The opportunity of molecular genetic testing if appropriate

# 4. Patient-reported outcomes in patients undergoing genetic investigation and counseling for familial Long QT syndrome and Hypertrophic cardiomyopathy

In contrast to measured physiological values, mortality and morbidity, patient-reported outcome measures assesses the patients' perspective of their own functional status and wellbeing (Dawson et al., 2010). The impact of measuring patient-reported outcomes may pertain to provision of important understanding of patients physical or psychological vulnerabilities that otherwise might be overlooked. Further it may give information on disease progression and results of interventions, and establishing a more common understanding between the patient himself and the health-care provider (Valderas & Alonso, 2008).

The patient-reported outcome measures may either be generic (measuring patients perception of their general health and wellbeing), disease-specific (measuring patients perception of their health and wellbeing in relation to specific conditions) (Dawson et al., 2010), or dimension-specific (exploring particular domains to greater depth) (Fayers & Machin, 2007a). The term patient- reported outcome indicates interest in a whole range of outcomes (Fayers & Machin, 2007; Doward & McKenna, 2004). The outcomes chosen for the present study were health status, general anxiety, depression, physical health, heart-focused anxiety, general health perceptions, self-efficacy, and satisfaction with genetic counseling.

A literature search in PubMed of journal articles published up to present time (October 2011) comprising either of the following search words in title or abstract; health status, quality of life, physical health, mental health, anxiety, depression, psychological distress, psychological, emotional distress, coping, self-efficacy, or satisfaction, and

comprising either Long QT syndrome, Hypertrophic cardiomyopathy or hereditary heart disease, and either hereditary, familial, family history, inherited or genetic in any field retrieved 86 articles. Only 17 of these articles present data on patient-reported outcomes from patients with familial LQTS or familial HCM, and only three of these were published before the present study was initiated, one of the latter was in Dutch language. A review of the remaining 16 patient-reported outcome studies (with regard to research question asked, sample characteristics, type of design, methods of measuring variables and key findings) is presented in Table 4.1.

Table 4.1 An overview of studies that assesses patient-reported outcomes in patients with familial Long QT syndrome or familial Hypertrophic cardiomyopathy in the period of 2000-2011(based on search in **Pubmed)**

| **Author** | **Research question** | **Sample** | **Type of design** | **Methods** | **Key finding** |
|---|---|---|---|---|---|
| Lane, RD et al. 2011 | To investigate if stressed individuals with greater emotional awareness would experience somatic symptoms in a more differentiated way independent of neuroticism | 161 LQTS patients | Descriptive<br><br>Cross-sectional<br><br>Ecological momentary assessments of symptoms over three days | Revised NEO Personality<br><br>Beck Depression Inventory (BDI)<br><br>Positive and Negative Affect Scale (PANAS)<br><br>10 vignettes describing emotion-provoking interactions | Patients that are more emotionally aware report somatic symptoms in a more differentiated way. |
| Hamang, A et al. 2010 | To investigate if there is a relationship between living with genetic risk of inherited arrhythmia and health status vulnerability and investigate the relationship between socio-demographic variables, clinical status and health status domains | 127 patients referred to genetic counseling because of familial LQTS or familial HCM | Descriptive<br><br>Cross-sectional | The Short Form 36 health survey (SF-36)<br><br>Clinical status<br><br>Socio-demographic variables | Patients reported significant lower SF 36 score as compared to the general population for the domain of general health |
| Christiaans, I et al. | To evaluate counselee's views and opinions on | 123 predictively | Descriptive | Opinions on information provision, | Genetic counseling was valued positively. |

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| 2009 | predictive genetic counseling and DNA testing, and the cardiac follow-up in HCM mutation carriers | tested HCM carriers | Cross-sectional | satisfaction with counseling, social pressure in DNA testing and regret of DNA testing, communication, nervous anticipation, reassurance, and general disadvantages | Carriers also had a positive attitude towards the cardiac follow-up, however there was a low frequency of patients receiving cardiac follow-up |
| Lane RD et al. 2009 | To determine whether the circumstances preceding an arrhythmic event differed from those preceding a prior control occasion | 38 LQTS patients | Case-crossover interview | 7- point scale used for rating peak happiness, general happiness, and stress and a 7 point scale used for rating exertion<br><br>Characteristics | Happiness was found associated with a reduction in the 24-hour risk of cardiac events, with stress having the opposite effect |
| Christiaans, I et al. 2008 | To assess long-term quality of life and psychological distress in HCM mutation carriers, and to identify socio-demographic, clinical, and risk and illness perception related factors associated to the outcomes | 228 proven carriers of a pathogenic mutation in one of the genes associated with HCM | Descriptive; A cross-sectional cohort study | The Short Form 36 health survey<br><br>The Hospital Anxiety and Depression Scale<br><br>Demographic variables<br><br>The revised version of the illness perception questionnaire | Levels of quality of life and distress were not impared compared to a general population<br><br>Illness and risk perception related variables were major determinants of quality of life and distress. |
| Meulenkamp, T.M. et al. 2008 | How does children that are mutation carriers perceive their carrier | 33 mutation carrier children of either LQTS, HCM or FH | Qualitative | Semi structured audiotaped interviews guided by Leventhals | Positive future health perceptions, but feelings of |

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|---|---|---|---|---|---|
| | status and what are the consequences they experience concerning life style modifications, medication use and worries | | | modell of self-regulation on<br><br>Illness perceptions, use of medication, lifestyle modifications, worries and coping | controllability varied, worries about dying and frustrations of being different. |
| Andersen, J et al. 2008 | To investigate the psychosocial aspects of living with LQTS | 7 individuals who had been tested for Long Qt genetic mutation | Qualitative design | In-depth interviews with a semi-structured interview guide on the topics; living with risk, family members, being sick or not sick, and healthcare services | Main concern was for their children's health, but experience of worries and limitations in their daily lives. |
| Giuffre, R.M. et al 2008 | To compare children with asthma to children with Long QT syndrome in terms of anxiety and medical fears | 7 children with Long QT syndrome. 40 children with asthma and their mothers | Comparative design | The Fear Survey Schedule for Children-Revised<br><br>The Revised Childrens Manifest Anxiety Scale<br><br>The Achenbach Child Behavior Checklist<br><br>The state-Trait Anxiety Inventory | Children with LQTS had significantly more internalizing problems, and their mothers had significantly more anxiety. |
| Hendriks, K et. Al. 2008 | To investigate the extent and course of distress caused by predictive genetic testing | 77 adult relatives of LQTS index patients in whome a causative mutation was detected and their | Prospective design with assessments 2 weeks after consultation , and 2 weeks and 18 months | Impact of event scale<br><br>Beck Depression inventory | Individuals who received an uncertain ECG seemed especially vulnerable for distress. In carriers and their |

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| | | partners n= 57 | after DNA disclosure | | partners disease-related anxiety remained elevated. |
| Ingles, J et al. 2008 | To identify the psychosocial factors that impact on the emotional well-being of those attending a speciality cardiac genetic clinic | 109 participants having a clinical diagnosis of HCM | Descriptive | Demographics<br><br>Hospital Anxiety and Depression Scale<br><br>A Patient Experience Scale<br><br>Patient Satisfaction Scales | HCM patients who attend specialized cardiac genetic clinics are better adjusted and worry less, then those who do not attend. Anxiety was predicted by adjustment to and worry about HCM. Depression was predicted by adjustment and location of patient follow-up |
| Smets, E et al. 2008 | How the quality of life of carrier children compares to the quality of life of their peers<br><br>To what extent the children's health-related quality of life and their parents perception thereof concurs | 30 families with familial hypercholesterolemia, hypertrophic cardiomyopathy and long QT syndrome, comprising 35 carrier children and 37 parents | Descriptive | Socio-demographic information<br><br>Children health-related quality of life (KIDSCREEN) | There were no differences found between the children and their peers.<br><br>Parents rated their child's psychological wellbeing lower than the child did. |
| Hoedemaekers, E et al. 2007 | To investigate the influence of two coping styles (monitoring and blunting) and perceived control on emotional | 114 adult family members of index patients with LQTS, DCM, HCM or ARVC offered | Prospective design with assessment after the first consultation, after test disclosure and 2 months after the test | Pearlin's Mastery List<br><br>The condition-specific Health Locus of | Less monitoring reflects less emotional distress before the outcome of genetic testing, while a stronger feeling of |

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|---|---|---|---|---|---|
| | distress in persons at risk of hereditary heart disease | genetic counseling | disclosure | Control (HLOC-) scale<br><br>Threatening Medical Situations Inventory (TMSI) | mastery reflects less emotional distress both before and after DNA test result. |
| Farnsworth, M et al. 2006 | To describe the experiences of parents who have a child or children with LQTS | 31 parents | Qualitative design | A secondary analysis of a phenomenological study open-ended questions about life with LQTS, including fear of death, quality of life, education and insurance | Fear of their children dying, different strategies to manage fear and frustrations about lack of knowledge of LQTS among health care providers |
| Hendriks, K et al. 2005 b | To assess levels of disease-related distress and situational anxiety and depression to find out to what extent parents were distressed 18 months after having received a DNA test result for LQTS in their children | 36 parents (17 parental couples an 2 single parents) who had applied for genetic testing of their children | Prospective design with assessments 2 weeks after consultation , and 2 weeks and 18 months after DNA disclosure | The Impact of Event Scale (IES)<br><br>The Spielberger State Anxiety Inventory (STAI-s)<br><br>Beck Depression Inventory (BDI) | Parents of carriers children reported more distress, also over time. High levels of distress in prior assessment, familiar with the disease for a longer time, experience of sudden death in the family, less educated and unsatisfied with the given information were predictors. |
| Hendriks, K et al. 2005 a | To assess the psychological effect of predictive testing in parents of children undergoing genetic | 36 parents (17 parental couples an 2 single parents) who were clinically diagnosed LQTS | Prospective design<br><br>assessments 2 weeks after consultation , and 2 weeks after DNA | The Impact of Event Scale (IES)<br><br>The Spielberger State Anxiety Inventory | 50% of the parents of carrier children showed clinically relevant high levels of distress. Parents who were |

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|---|---|---|---|---|---|
| | testing of LQTS<br><br>The effect of carrier status of the parent on parental levels of distress<br><br>The effect of the composition of test results in a family on levels of parental distress | patients with a mutation positive result and partners | disclosure | (STAI-s)<br><br>Beck Depression Inventory (BDI) | familiar with the disease for a longer time, who had more experience with the disease, and received a positive test result for all their children were most distressed. |
| Cox et al. 1997 | To assess the health related quality of life and psychological wellbeing of patients with hypertrophic cardiomyopathy, and to correlate these with symptoms, clinical, and psychosocial factors. | 137 hypertrophic cardiomyopathy patients | Descriptive | Short Form 36 Health survey (SF-36)<br><br>Hospital Anxiety and Depression Scale (HADS)<br><br>Adjustment and worry about Hypertrophic cardiomyopathy<br><br>Patient satisfaction<br><br>Clinical data | HCM is associated with with substantial restrictions in Health related quality of life. Symptoms, adjustment, and quality of interaction with clinical staff contribute to these limitations. |

## 4.1 Health status

The World Health Organization (WHO, 1948) defines health to be, not only absence of disease, but a "state of complete physical, mental and social well-being". There is general consensus that health consists of these three aspects of well-being, however there are big variations across studies as to how to define health, and most investigators avoid the definitions and let the health domains speak for themselves (Fayers & Machin, 2007).

The present study chose to include both physical and mental health domains as measured by SF-36 Health Survey (Ware, Jr. & Gandek, 1998). This measure has been used extensively in health research. In accordance with WHOs definition of health, SF-36 measures not only health functioning but also well-being. Health functioning is according to SF-36 literature, the extent to which health limits the patient in physical, social and role activities. Perceived wellbeing is defined as frequency and intensity of feeling states including general mental health, bodily pain and vitality. In addition, patient perception of health in general is included in the health concept. Including perceived general health may be a strength, given critical arguments of that health status questionnaires mainly assess domains that are of clinical importance, but that may not be the concern of the patient (Doward & McKenna, 2004). For example no major differences were found in physical and mental health domains of children at risk of inherited cardiac disorders compared to peers (Smets et al., 2008). However, other research has found that children in this situation may feel a loss of control, worries about dying, and frustrations of being different (Meulenkamp et al., 2008; Giuffre et al., 2008; Meulenkamp et al., 2008), all of which most likely will affect the general perception of health.

Previous research has shown that several clinical variables may affect health in patients with familial cardiac disorders. With regard to the adult population clinically affected with LQTS or HCM, health status has been measured quantitatively in HCM patients (Christiaans et al., 2009b; Cox et al., 1997), and has been described qualitatively in LQTS patients (Andersen et al., 2008). The results from these investigations showed that HCM patients had major impairments in both physical and mental health domains. LQTS patients experienced daily limitations such as having to rest and not being able to work because of symptoms of fatigue, exhaustion, palpitations and headaches (Andersen et al., 2008).

Health status has been strongly related to symptom patterns, although not consistently. In one of the studies of HCM patients, both affected and unaffected patients were included, comparing patient-reported outcomes in patients with clinical diagnosis and patients at genetic risk for HCM in terms of predictors of physical health, mental health and psychological distress (Christiaans et al., 2009b). The presence of a clinical diagnosis or HCM related symptoms were strongly related to impaired physical health. However, for both groups perceptions of risk and carrier-ship (perceived risk of sudden cardiac death, or belief in serious consequences, or symptoms) greatly affected physical and mental health as well as anxiety and depression levels. Thus there is a need to further explore the health status in patients with familial cardiac disorders.

## 4.2 General anxiety and depression

General anxiety is most often associated with the emotion of fear, involving feelings of tension, worry, apprehension, and dread for something perceived as threatening in the future (Stein & Hollander, 2002), while depression is usually described as an emotion of sadness, with feelings of sorrow, hopelessness, gloom, lack of energy and adhedonia (Watson et al., 1995). Standard classification of mental disorders is

described and specified in the International Classification of Diseases ICD-10 (World Health Organisation., 1992), or the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-IV) (American Psychiatric Association, 1987), which views anxiety and depression as discrete psychopathological disorders. In contrast to this categorical approach, the dimensional approach views symptoms of anxiety and depression as normal responses to demands and threats measured on a continuum from absence to maximum intensity (Bjelland & Dahl, 2008). In the present study the Hospital Anxiety and Depression scale dictates a categorical approach (Zigmond & Snaith, 1983).

Addressing the psychological consequences of LQTS predictive testing in a longitudinal study, general anxiety and depression levels were found to be close to that of the normal population within 18 months after testing (Hendriks et al., 2008). Depression levels were lower among those who were more satisfied with follow up, thus HCM patients that attend follow up seem better adjusted and have less worry (Cox et al., 1997; Ingles et al., 2008). How general anxiety and depression levels compares to expected scores of the general population should be further investigated in patients referred to genetic investigation and counseling for familial LQTS or familial HCM. Further there is a need to investigate whether general anxiety and depression differ between LQTS and HCM patient groups.

## 4.3 Heart-focused anxiety

In this study heart-focused anxiety is defined as the specific fear of cardiac-related stimuli and sensation based on the perception that symptoms will be harmful, causing i.e. serious arrhythmias or sudden cardiac death (Eifert et al., 2000a).

Responding to cardiac-related stimuli and sensations with cardio-protective avoidance, heart-focused attention, and fear about heart sensations is associated with the presence of heart-focused anxiety (Eifert, 2000a). The concept is identified as a psychological process variable related to heightened anxiety levels (Eifert et al., 2000b). Heart-focused anxiety was originally identified as a psychological problem closely related to anxiety sensitivity and "cardiophobia" among patients without actual heart disease (Eifert, 1992; Eifert & Forsyth, 1996a; Eifert et al., 1996b), but has also been shown to be a relevant psychological variable to study in patients with actual heart-disease (Hoyer et al., 2008). Based on that levels of anxiety increase among patients with actual cardiac disease after receiving a diagnosis, and that physical healthy patients can be as concerned as patients with a justifiable concern about heart disease, previous findings indicate that heart-focused anxiety also may be an individual difference factor (Eifert et al., 2000b; Eifert, 1992).

A conceptual and clinical review of heart-focused anxiety and chest pain suggest that responding fearful to cardiac-related stimuli and sensations may be part of a vicious circle that not only creates even higher levels of cardio-protective avoidance, heart-focused attention, and fear about heart sensations, but also may contribute to greater levels of perceived pain, disability, and future episodes of elevated anxiety or panic (Eifert, 2000b). Therefore it is necessary to find out how symptoms of heart-focused anxiety relate to general anxiety, depression and physical health in the present patient-group.

Heart-focused anxiety may be explained by previous learning conditions relating to separation issues and cardiac disease, psychological vulnerability, negative events, as well as genetic and acquired biological vulnerability factors (Eifert, 1992).

LQTS patients participating in a qualitative study reported daily limitations and anxiety because of their disorder (Andersen et al., 2008). Perceived symptoms or

family members worrying about them caused them to avoid certain activities. Uncertainty, unresolved emotions and worries about other relatives at risk caused anxiety (Andersen et al., 2008). A study showed that self-reported emotional stress are related to cardiac events in LQTS patients, while positive emotions may be protective for the arrhythmia risk (Lane et al., 2009), thus more knowledge of psychological issues in affected individuals, is of utmost importance.

Although, general anxiety and depression levels seem to subside over time, disease-related anxiety has been reported to remain high over time (Hendriks et al., 2008). What factors influence heart-focused anxiety over time needs to be explored.

## 4.4 Self-efficacy expectations

Defined by Bandura, self-efficacy is the individual's capabilities to exercise control over events that affects his or her life (Bandura, 1977). Efficacy expectations and outcome expectations are important components of self-efficacy. Efficacy expectations pertain to a person's beliefs about his or hers ability to perform the behavior that will produce an expected outcome, while outcome expectations pertain to believing in that a certain behavior will produce a specific outcome. Self-efficacy is strongly related to stress, coping and health and may determine whether specific health behaviors are initiated and maintained. The amount of stress and depression in individuals when facing a health threat is determined by their own beliefs about their coping abilities (Siela & Wieseke, 2000). Self-efficacy can be general or domain specific. In the present study self-efficacy is defined as the individual's beliefs or expectations in coping with cognitive, emotional, and behavioral aspects in relation to the genetic counseling. A feeling of less personal control have previously been shown to predict higher level of distress both before and after genetic testing in persons at risk for

different familial cardiac disorders (Long QT syndrome, Hypertrophic cardiomyopathy, Dilated cardiomyopathy or Arrhythmogenic right ventricle cardiomyopthy)(Hoedemaekers et al., 2007). Therefore, the role of patients' self-efficacy expectations should be further explored.

## 4.5 Satisfaction with genetic counseling

Patient satisfaction is a significant issue in evaluating medical care (Shiloh et al., 1990). In the genetic counseling setting it has been emphasized that there is a need to assess satisfaction, in order to develop and improve counseling services for the patients (Demarco et al., 2004). Typically, patient satisfaction comprises several aspects, such as instrumental, affective and procedural satisfaction. The present study defines satisfaction with genetic counseling as the patient satisfaction with the counselors' skills of providing medical information (instrumental satisfaction), ability to provide psychological support (affective satisfaction), and to satisfaction with the situational factors of logistics and practical matters (procedural satisfaction)(Shiloh et al., 1990).

Genetic counseling has previously been valued positively among predictively tested HCM mutation carriers (Christiaans et al., 2009a), and satisfaction with time spent in the clinic, and satisfaction with communication in the clinic has been related to lower levels of depression among patients with HCM. However the role of satisfaction with genetic counseling in relation to patients' anxiety is to our knowledge not studied in the present patient groups.

## 4.6 State of the art (summary)

Previous research and clinical experience have identified health- related and psychological vulnerabilities in patients with a clinical diagnosis of LQTS or HCM, as well as in individuals at genetic risk of LQTS or HCM (Aatre & Day, 2011). However, there is still a need for better understanding of the effect of the conditions themselves in terms of self-reported health status, as well as a need to explore some of the psychological effects (general anxiety and depression) of living with this health threat, and further to find out how these patient-reported outcomes are influenced by other factors. There is also a need to identify emotional reactions related to living with the risk of serious arrhythmias and sudden cardiac death. Heart-focused anxiety may be a particular concern for this population. Although several studies have reported cardiac symptoms to be strongly related to emotional distress, none have focused on that living with fear of cardiac symptoms may increase general anxiety and influence the health in individuals who are living with the risk of serious arrhythmias and sudden cardiac death. The previous literature has identified factors such as perceived control and satisfaction with genetic counseling as important variables in relation to distress among these patients. To our knowledge no studies exist on what factors predispose or may be important for the prognosis of heart-focused anxiety in individuals with familial LQTS or familial HCM who receives genetic investigation and counseling.

# 5. Aims

## 5.1 Overall aim

The overall aim of this study was to obtain more knowledge about the health status, levels of general anxiety and depression, and symptoms of heart-focused anxiety in individuals living with the risk of serious arrhythmias and sudden cardiac death, receiving genetic investigation and counseling because of familial LQTS or familial HCM. Figure 5.1 shows investigated variables and proposed relationships.

## 5.2 Specific aims

The aims of the various papers comprising this study are:

Paper I Baseline

1. To examine if there is a relationship between living with genetic risk of inherited arrhythmia and health status vulnerability.
2. To explore relationship between socio-demographic variables, clinical status and health status domains among the patients coming to genetic counseling.

Paper II Baseline

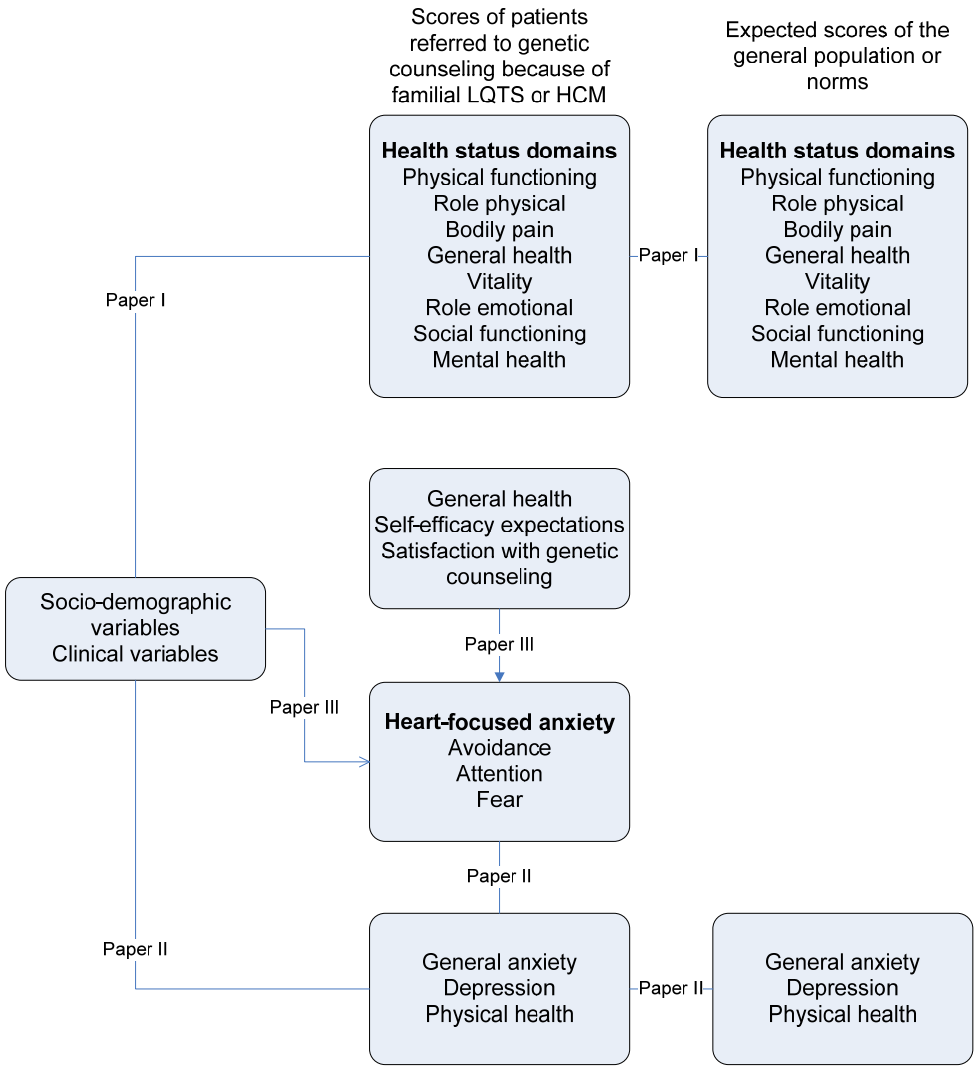
3. To investigate these patients' level of general anxiety, depression and physical health and compare the scores to expected scores of the general population.
4. To investigate the scores of general anxiety, depression, physical health, and heart-focused anxiety (avoidance, attention, fear) in patients referred because of familial LQTS as compared to the scores of patients referred because of familial HCM.

5. To assess the role of heart-focused anxiety (avoidance, attention and fear symptoms) in relation to general anxiety, depression, and physical health.

Paper III Follow-up

6. To assess heart-focused anxiety in patients with a clinical diagnosis of LQTS or HCM as compared to patients at genetic risk of LQTS or HCM, measured by the levels of cardio-protective *avoidance*, heart-focused *attention*, and *fear* about heart sensations.
7. To investigate the independent influence on heart-focused anxiety by the following putative predisposing factors; sudden cardiac death in close relatives, a recent cardiac death of a relative; patient knowing whether other relatives previously have undergone genetic testing; and by factors of possible prognostic importance; perceived general health, self-efficacy expectations; and satisfaction with genetic counseling (affective, instrumental, procedural aspects); while controlling for effects of questionnaire time points, patient gender, a clinical diagnosis of LQTS or HCM, and the result of genetic testing.

Figure 5.1 Model showing investigated relationships of the patient-reported outcomes, socio-demographic variables and clinical variables of patients referred to genetic counseling because of familial LQTS or familial HCM, and the comparisons made between the scores of the study group, expected scores, or norms of the general population.



# 6. Methods

## 6.1 Study Designs

In order to respond to the aims of the study, the following designs were applied in this multi-centre study:

- *A cross-sectional design* was used to investigate socio-demographic factors related to health status domains (Paper I), and to explore if three distinct symptoms of heart-focused anxiety (cardio-protective avoidance, heart-focused attention and fear about heart sensations) would be related to levels of general anxiety, depression, and physical health (Paper II).
- *A comparative design* was used to compare SF-36 health status scores of patients with familial LQTS or familial HCM (i.e. total sample of patients with familial LQTS or familial HCM; patients at genetic risk of LQTS or genetic risk of HCM; patients with a diagnosis of LQTS; patients with a diagnosis HCM) to that of expected scores of the Norwegian general population, and to compare scores according to clinical status (patients at genetic risk of LQTS or at genetic risk of HCM; diagnosis of LQTS; diagnosis of HCM) (Paper I), to compare general anxiety and depression scores to expected scores of Norwegian general population, and physical health to US SF-36 norms, and to compare general anxiety, depression, physical health, and heart-focused anxiety according to familial disorder (LQTS or HCM)(Paper II), and to compare levels of cardio-protective avoidance, heart-focused attention and fear about heart sensations in patients at genetic risk of LQTS or genetic risk of HCM as compared to patients with a diagnosis of LQTS or diagnosis of HCM (Paper III).
- *A prospective design* with measurement 2 weeks before genetic counseling, and at three time points after the genetic counseling (4 weeks, 6 months and 1 year

after counseling) was used to explore relationships between possible predictors as measured before, right after genetic counseling and 6 months after genetic counseling) and the course and outcome of cardio-protective avoidance, heart-focused attention and fear about heart sensations (Paper III).

## 6.2 Sample

The study comprised three samples; a consecutive sample consisting of patients who was referred or self-referred for genetic investigation and counseling because of either familial LQTS or familial HCM, and two reference populations that were used to calculate expected scores of the Norwegian general population. In addition SF-36 US norms were used.

*Patients*

The patients were family members and other appropriate relatives subsequently following the identification of a LQTS or HCM- causative mutation in an index case or individuals in whom a cardiologist had established or suspected a clinical diagnosis of LQTS or HCM. Patients were over 17 years of age, not previously genetic tested for a familial cardiac disorder, and were consecutively referred or self-referred to genetic counseling at the medical genetic departments in Trondheim, Bergen and Oslo. One hundred and seventy three patients were consecutively asked to participate in the study. A total of 127 patients returned the first questionnaire (one patient was excluded from this number in paper II and III because of not answering relevant questions in questionnaire), which corresponds to a response rate of 73.4% (T1). Patients dropped out during follow-up. Immediately after genetic counseling (T3) 122 patients filled in the questionnaire, after four weeks (T4) 85 patients responded, after 6 months (T5) 65 patients responded, and finally the 1-year follow up (T6) comprised 68 patients. The explanation for how the number of patients can increase from one point to the next (as from T5 to T6) is that some participants were non-responders at T5, but responded at T6. An overview of the number of participants and patient-reported outcome measures

at the various assessment times is given in figure 6.1. The characteristics of the patients who did and did not complete the one year follow-up questionnaire at T6 did not differ significantly for any of the variables.

*Reference populations*

The reference populations were based on**;**

1) Normative data from the general Norwegian population. SF-36 expected scores were calculated based on the data from the Short Form 36 (SF-36) health survey (Loge & Kaasa, 1998). From the 3500 questionnaires sent out, a total of 2323 (67%) Norwegian individuals aged 19-80 filled in and returned the questionnaire. Expected scores of the general population were calculated based on age and gender of the patients**.**

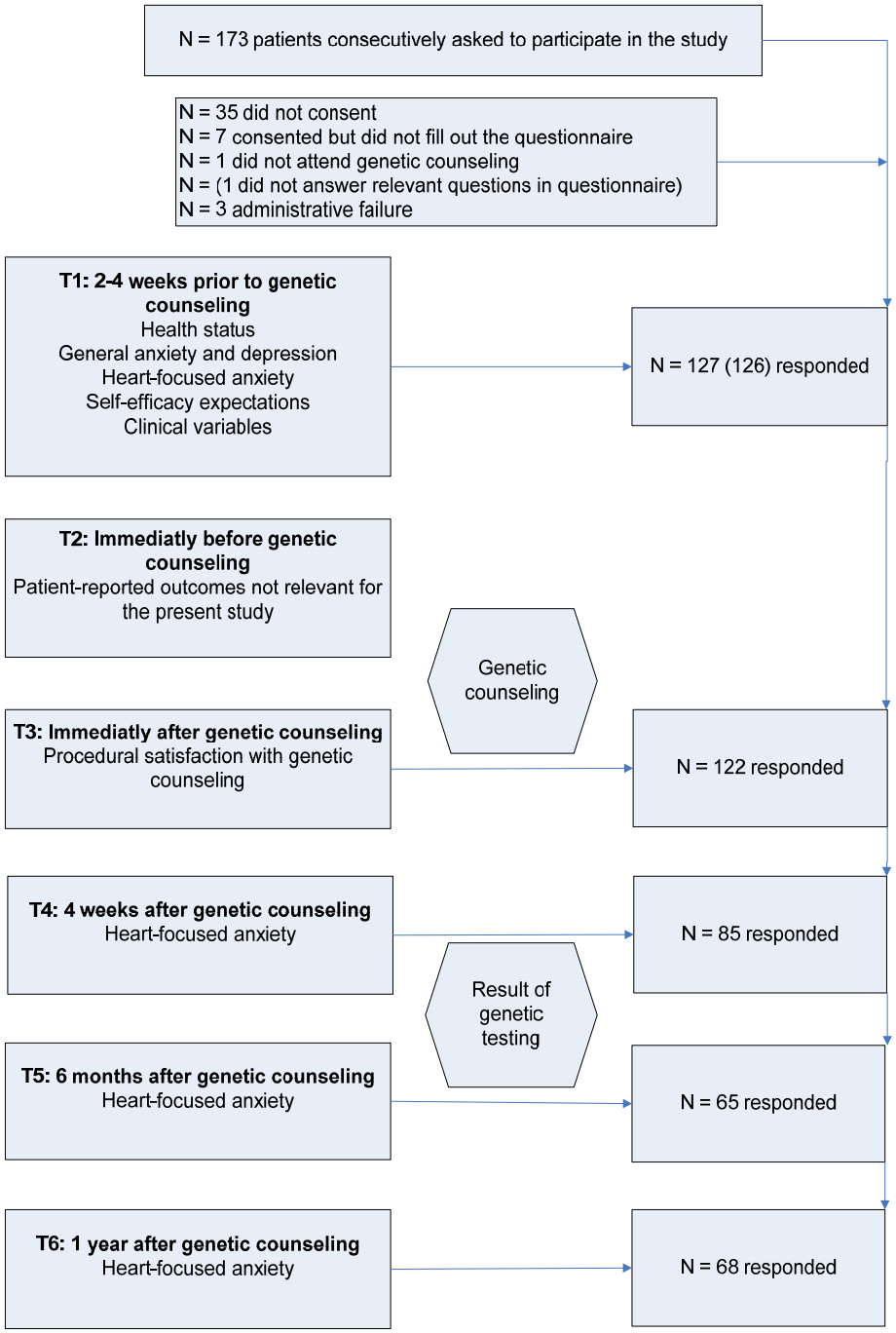
2) Expected scores of general anxiety and depression were calculated based on normative data from the HUNT 2 study (Holmen et al., 2003). A total of 54867 subjects aged ≥20 years with complete data on Hospital Anxiety and Depression scale (HADS), smoking and education variables, and without self- reported previous cardiovascular disease was included in the reference population that formed the basis of the regression formula. Expected scores were calculated based on age, gender, educational level and smoking habits.

3) US physical health norms according to SF-36 norm-based scoring were used, when comparing the physical health scores in the study with a general population (Ware, 2001).

## 6.3 Procedure

Ethical approval was obtained from the Regional Committee for Medical Research Ethics in Western Norway in September 2004. Data was collected as part of a prospective study on the psychosocial implications of diagnosis and counseling in hereditary diseases. Information about the study was mailed to the patient together with a consent form and the first questionnaire. The participants received one reminder. Participants completed measures of health status, general anxiety, depression, heart-focused anxiety, self-efficacy expectations, and satisfaction with genetic counseling. Questionnaires were collected 2-4 weeks prior to the genetic counseling (T1) and 4 weeks (T4), 6 months (T5) and one year after genetic counseling (T6). The participants also received a questionnaire immediately prior to (T2) and after the genetic counseling session (T3).

Figure 6.1 An overview of the patient-reported outcome measures and number of participants at various assessment times



## 6.4 The patient-reported outcome measures

Data on health status domains, general anxiety and depression, heart- focused anxiety, self-efficacy expectations, and satisfaction with genetic counseling were obtained from patient-reported outcome measures. An explanation of the various patient reported outcome measures is provided in table 6.1.

### 6.4.1 Short Form-36 Health Survey (SF-36)

SF-36 is a self-report questionnaire that measures health status (0 = worst health state. 100 = best health state) on eight sub-scales measuring physical domains (physical functioning, role limitation-physical, bodily pain, general health), and mental domains (vitality, social functioning, role limitation-emotional, mental health) (Ware & Kosinki, 2001). An additional point reports changes in health over the last year. The physical domains form the basis to calculate a physical component summary (PCS) and the mental domains may be calculated into a mental component summary (MCS). The questionnaire is generic and multidimensional and it is suitable for administration to large populations and to subgroups such as patients. Its purpose is to be a measure of health status or health outcome in cross-sectional and longitudinal studies (Hutchinson et al., 1997).

SF-36 was chosen to be the health status measure to be translated in The International Quality of Life Assessment (IQOLA) Project, where the goal was to develop and validate translations of the health status measure for use in multinational clinical trials and other international studies of health (WareJr. & Gandek, 1998). The Norwegian translation of the acute version was used in the present study with a 1-week recall period (Ware et al., 2001).

### 6.4.2 The Hospital Anxiety and Depression Scale (HADS)

The HADS measures symptoms of anxiety and depression on two subscales; HADS-depression (7 items), and HADS-anxiety (7 items) (Zigmond & Snaith, 1983), and has been developed not to be influenced by physical symptoms. A higher score means a higher level of anxiety or depression (scores ranging from 0-21). It is well suited as a screening tool for anxiety and depression, also in patients suffering inherited heart diseases, with a cutoff score of 8 to detect cases (Poole & Morgan, 2006). A Norwegian translation was available.

### 6.4.3 The Cardiac Anxiety Questionnaire (CAQ)

The CAQ consists of 18 items in three subscales pertaining to a) avoidance of activities believed to elicit cardiac symptoms (avoidance) b) heart-focused attention and monitoring of cardiac activity (attention) and, c) fear and worry about chest and heart sensations and functioning (fear) (Eifert et al., 2000a). Each item is rated on a 5–point likert scale; indicating how frequently the behavior or symptoms typically occurs, ranging from 0 = never to 4 = always. The questionnaire was translated to Norwegian by a professional translator with forward and backward translation procedure. Subscales, item text, item number and interpretations of the subscales is found in paper III, box 1.

### 6.4.4 The Bergen Genetic Counseling Self-efficacy Scale (BGCSES)

The BGCSES measures self-efficacy expectations related to genetic counseling. The scale comprises of 21 items describing tasks and challenges that are likely to occur during and after genetic counseling, and the individual's beliefs that he or she will be able to cope with these. Each item was rated on a scale from 0-10 (0=cannot do at all,

10 = can do without difficulty). The average total sum score of the scale was used. The BGCSES has been developed using the guidelines of Bandura for constructing Self-efficacy Scales (revised 2001) Albert Bandura, Stanford University, Palo Alto, CA, USA, by a panel of medical geneticists, genetic counselors, and psychologists and has been used in related studies (Bjorvatn et al., 2008; Bjorvatn et al., 2009).

### 6.4.5 Satisfaction with Genetic Counseling

The patient's satisfaction with the genetic counseling was filled in immediately after the genetic counseling session. The scale is a 9-item measure which has three subscales measuring instrumental, affective and procedural satisfaction (range 3-12) (Shiloh et al., 1990). Higher scores indicate greater satisfaction. A Norwegian translation was available.

## 6.5 Socio-demographic and clinical variables

The socio-demographic variables were age, gender, marital status, number of biological children, employment and education status, and referral by physician/self-referral through family member. The socio-demographic variables were collected from the baseline questionnaire (T1), together with self-constructed questions regarding family history of sudden cardiac death, and if the patients knew whether other relatives had previously undergone genetic testing (yes, no, uncertain). The rest of the clinical variables (having a clinical diagnosis of LQTS, having a clinical diagnosis of HCM, and number of patients detected to be mutation carriers) were collected from the patients' medical record.

Table 6.1 Explanation of the patient reported outcome measures; Questionnaire, including subscales, summary of contents, number of items, range and total range

| Questionnaire | | Subscale | Summary of contents | Items | Range | Total range |
|---|---|---|---|---|---|---|
| SF-36 | Physical health | Physical functioning | Extent to which health limits physical activities such as self-care, walking, climbing stairs, bending, lifting, and moderate vigorous exercises | 10 | 1-3 | 0-100 (transformed) |
| | | Role physical | Extent to which physical health interferes with work or other daily activities, including accomplishing less than wanted, limitations in the kind of activities, or difficulty in performing activities | 4 | 1-2 | |
| | | Bodily pain | Intensity of pain an effect of pain on normal work, both inside and outside the home | 2 | 1-6 | |
| | | General health | Personal evaluation of health, including current health, health outlook, and resistance to illness | 5 | 1-5 | |
| | Mental health | Vitality | Feeling energetic and full of pep versus feeling tired and worn out | 4 | 1-6 | |
| | | Social functioning | Extent to which physical health or emotional problems interfere with normal social activities | 2 | 1-5 | |
| | | Role emotional | Extent to which emotional problems interfere with work or daily activities, including decreased time spent on activities, accomplishing less, and not working as carefully as usual | 3 | 1-2 | |
| | | Mental health | General mental health, including depression, anxiety, behavioural-emotional control, general positive affect | 5 | 1-6 | |
| | | Health transition | Evaluation of current health compared to one year ago | 1 | 1-5 | |
| | | Total | | 36 | | |

| | | | | | |
|---|---|---|---|---|---|
| HADS | Anxiety | Restlessness and worry, as in generalized anxiety disorder, plus one item on panic attacks | 7 | 0-3 | 0-21 |
| | Depression | Reduced pleasure response, in addition to psychomotor retardation and depressed mood | 7 | 0-3 | |
| | Total | | 14 | | |
| CAQ | Avoidance | Avoidance of activities believed to elicit cardiac symptoms | 5 | 0-4 | 0-4 |
| | Attention | Heart-focused attention and monitoring of cardiac activity | 5 | 0-4 | |
| | Fear | Fear and worry about chest and heart sensations and functioning | 8 | 0-4 | |
| | Total | | 18 | | |
| BGCSES | | Self-efficacy beliefs related to the ability to process and recall the information given, to maintaining emotional control, and related to the consequences of the counselling session | 21 | 0-10 | 0-10 |
| SCS | Instrumental | The extent to which the respondent evaluates that the counsellor has the required skills, and gives the required treatment and reassurance | 3 | 1-4 | 3-12 |
| | Affective | Evaluation of the counsellors behaviour toward the patients as a person rather than a case devoting time, showing interest and devotion | 3 | 1-4 | |
| | Procedural | Satisfaction with the administrative procedures like waiting time, bureaucratic arrangements, and conduct of administrative staff | 3 | 1-4 | |

SF-36 = Short Form 36, HADS = Hospital Anxiety and Depression scale, CAQ = Cardiac Anxiety and Depression scale, BGCSES = The Bergen genetic counselling self-efficacy scale, SCS = Satisfaction with Genetic Counselling Scale

## 6.6 Statistical methods

The statistical analyses was performed with SPSS version 15 (Paper I), and 18 (Paper II and III) (SPSS Inc., Chicago, IL, USA). Statistical significance was assessed with two-sided $P < 0.05$. Depending on the research questions and the variables different types of statistical methodology were used.

***Descriptive statistics***

Descriptive analyses have been used in all papers to describe the sample based on mean values, standard deviations or standard error of mean, and ranges. SF-36 expected scores for each of the respondents were calculated for all health status domains based on the normative data from the Norwegian population register (Loge & Kaasa, 1998), controlling for age and sex (Paper I). Expected values for HADS were based on Norwegian reference population data (Holmen et al., 2003), with formula controlling for age, sex, educational level and smoking habits (Paper II). Preliminary analyses were conducted to assess missing data, normality, and checking for outliers. *Cronbach's alpha* was computed to determine the internal consistency reliability for all questionnaires applied in the study.

***Statistical techniques to compare groups***

The *unpaired t–test* was used to compare mean values,, the *chi-square test* for proportions, and the *Mann-Whitney U test* for median values between independent groups. The *paired t-test* was used to compare means with repeated measures and to compare mean values to expected scores. *One-way analysis of variance (ANOVA) with post hoc comparisons* was used to test differences in the mean scores between three groups.

***Statistical techniques to explore relationships among variables***

*Spearman rank correlation* was used to explore correlations between the variables.

*Multiple linear regression analyses* were used to explore relationship between socio-demographic, clinical status and health status domains. *Hierarchical regression analyses* were used to assess the role of heart-focused anxiety (avoidance, attention and fear symptoms) in relation to general anxiety, depression and physical health, beyond relevant covariates. *Mixed linear modelling (MLM)* was used to investigate the independent influence on heart-focused anxiety by the following putative predisposing factors; sudden cardiac death in close relatives, a recent cardiac death of a relative; patient knowing whether other relatives previously have undergone genetic testing; and by factors of possible prognostic importance; perceived general health, self-efficacy expectations; and satisfaction with genetic counseling (affective, instrumental, procedural aspects); while controlling for effects of questionnaire time points, patient gender, a clinical diagnosis of LQTS or HCM, and the result of genetic testing.

All predictors were entered into MLMs to assess both their main effects and their possible interaction with time.

## 6.7 Ethical considerations

The present study has followed the ethical guidelines of the Declaration of Helsinki (World Medical Association 1983. Approval from the Regional Committee for Medical Research Ethics, Western Norway was obtained 01.09.04 (REK VEST # 128.04). In addition, the study was approved by the Norwegian Social Science Data Services (# 11289).

Three primary ethical principles for protecting study participants are beneficence, respect for human dignity, and justice (Polit & Beck, 2008). To protect the study participants' rights, procedures were followed to ensure that the individuals were

guaranteed anonymity and the right to withdraw from the study at any time. The participants were provided with a letter with information needed to make a reasoned decision about participation in the study, and additionally a consent form had to be actively returned together with the first questionnaire. In a risk/benefit assessment it was concluded that there was no high risk that participation in the study should lead to any physical or psychological harm. However, the study provided possibility to refer patients to a psychologist specialist if that was deemed necessary. The study conformed to that patients have the right to fair treatment, and in accordance with the biotechnology act that states that patients undergoing predictive genetic testing should be provided with genetic counseling (Act of biotechnology in human medicine, 2003, appendix), all patients were given the same intervention if they participated in the study or not.

# 7. Results

A summary of the individual papers I-III with main results are presented in the following chapters.

## 7.1 Sample characteristics

Socio-demographic and clinical variables of the sample are shown in Table 7.1. The mean age was 45 years (range: 17-83), most were married or cohabitating (77.2 %), had children (78.0 %), and were employed (67.7 %). Few had a clinical diagnosis of LQTS (9.4%) or HCM (15.7 %). Approximately half of the sample (44.9 %) reported that there had been a sudden cardiac death in a relative. More than half of the patients (60.6%) knew that other relatives previously had undergone genetic testing. One hundred and thirteen patients (89.0 %) were offered and consented to genetic testing. The result of genetic testing in the current sample showed that a mutation was detected in 44 individuals (34.6 %). Descriptive information of the patient-reported outcomes are presented in table 7.2.

Table 7.1 Socio-demographic variables and clinical variables of 127 individuals with familial Long QT syndrome or familial hypertrophic cardiomyopathy who received genetic investigation and counseling in Norway in the years 2005-2007

| **Variable** | Total | % | Familial LQTS | % | Familial HCM | % | p-value |
|---|---|---|---|---|---|---|---|
| | n =127 | 100 | n =88 | 100 | n =39 | 100 | |
| **Sex** | | | | | | | 0.012[a] |
| Female | 68 | 53.5 | 54 | 61.4 | 14 | 35.9 | |
| Male | 59 | 46.5 | 34 | 38.6 | 25 | 64.1 | |
| **Age Groups** | | | | | | | 0.025[b] |
| 29 or less: | 26 | 20.5 | 22 | 25.0 | 4 | 10.3 | |
| 30-39: | 20 | 15.7 | 14 | 15.9 | 6 | 15.4 | |
| 40-49: | 31 | 24.4 | 21 | 23.9 | 10 | 25.6 | |
| 50-59: | 27 | 21.3 | 20 | 22.7 | 7 | 17.9 | |
| 60-69: | 11 | 8.7 | 4 | 4.5 | 7 | 17.9 | |
| 70 or more: | 12 | 9.4 | 7 | 8.0 | 5 | 12.8 | |
| **Marital status** | | | | | | | 0.590[a] |
| Married/cohabitant | 98 | 77.2 | 70 | 79.5 | 28 | 71.8 | |
| Single | 17 | 13.4 | 11 | 12.5 | 6 | 15.4 | |
| Divorced/separated | 7 | 5.5 | 4 | 4.5 | 3 | 7.7 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Widow/widower | 4 | 3.1 | 2 | 2.3 | 2 | 5.1 | |
| Missing | 1 | 0.8 | 1 | 1.1 | | | |
| **Children** | | | | | | | 0.161[a] |
| Have children | 99 | 78.0 | 65 | 73.9 | 34 | 87.2 | |
| Missing | 2 | 1.6 | 2 | 2.3 | | | |
| **Employment** | 86 | 67.7 | 61 | 69.3 | 25 | 64.1 | 0.538[a] |
| Missing | 1 | 0.8 | 1 | 1.1 | | | |
| **Education status** | | | | | | | 0.417[a] |
| Primary school | 26 | 20.5 | 21 | 23.9 | 5 | 12.8 | |
| High school | 64 | 50.4 | 42 | 47.7 | 22 | 56.4 | |
| College/university | 37 | 29.1 | 25 | 28.4 | 12 | 30.8 | |
| Missing | | | | | | | |
| **Sudden cardiac death occurred in family** | | | | | | | 0.259[a] |
| Sudden Death | 57 | 44.9 | 39 | 44.3 | 18 | 46.2 | |
| Missing | 25 | 19.7 | 13 | 14.8 | 12 | 30.8 | |
| **Patients knowing whether other relatives** | | | | | | | <0.001[a] |
| **previously had undergone genetic testing** | 77 | 60.6 | 64 | 72.7 | 13 | 33.3 | |
| Missing | 14 | 11.0 | 11 | 12.5 | 3 | 7.7 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Referral** | | | | | | | <0.001[a] |
| By physician | 35 | 27.6 | 15 | 17.0 | 20 | 51.3 | |
| Self referred through family | 90 | 70.9 | 71 | 80.7 | 19 | 48.7 | |
| Missing | 2 | 1.6 | 2 | 2.3 | | | |
| **Clinical Status** | | | | | | | <0.001[a] |
| Clinical diagnosis of LQTS or HCM | 31 | 24.4 | 12 | 9.4 | 19 | 15.0 | |
| Diagnosis of both LQTS and HCM | 1 | 0.8 | | | 1 | 0.8 | |
| No diagnosis | 95 | 74.8 | 76 | 86.4 | 19 | 48.7 | |
| **Type of genetic test offered** | | | | | | | <0.001[a] |
| Predictive | 82 | 64.6 | 68 | 77.3 | 14 | 35.9 | |
| Diagnostic | 31 | 24.4 | 13 | 14.8 | 18 | 46.2 | |
| Missing | 14 | 11 | 7 | 8.0 | 7 | 17.9 | |
| **Result of genetic investigation** | | | | | | | 0.086[a] |
| Mutation positive result | 44 | 34.6 | 36 | 40.9 | 8 | 20.5 | |
| Mutation negative result | 69 | 54.3 | 45 | 51.1 | 24 | 61.5 | |
| Missing | 14 | 11.0 | 7 | 8.0 | 7 | 17.9 | |

[a]Exact two sided chi-square test, [b]Wilcoxon-Mann-Whitney test.

Table 7.2 Descriptive information of the patient- reported outcomes

| **Questionnaires** | Time point | N | Mean | SD | SEM | Min/max | Cron-bach's alpha |
|---|---|---|---|---|---|---|---|
| **Short Form 36 (SF-36)** | | | | | | | |
| Physical functioning | T1 | 122 | 88.18 | 16.35 | 1.48 | 28.57-100.00 | 0.87 |
| Role physical | T1 | 126 | 78.24 | 35.54 | 3.17 | 0.00-100.00 | 0.89 |
| Bodily pain | T1 | 127 | 78.34 | 25.91 | 2.30 | 0.00-100.00 | 0.92 |
| General health | T1 | 126 | 69.54 | 20.54 | 1.83 | 0.00-97.00 | 0.71 |
| Vitality | T1 | 127 | 55.73 | 24.80 | 2.20 | 0.00-100.00 | 0.91 |
| Social functioning | T1 | 127 | 83.37 | 22.88 | 2.03 | 0.00-100.00 | 0.88 |
| Role emotional | T1 | 124 | 77.82 | 36.85 | 3.31 | 0.00-100.00 | 0.87 |
| Mental health | T1 | 127 | 76.30 | 19.47 | 1.73 | 4.00-100.00 | 0.90 |
| PCS | T1 | 120 | 50.55 | 8.61 | 0.79 | 24.87-64.28 | 0.88 |
| MCS | T1 | 120 | 48.93 | 11.63 | 1.06 | 6.41-63.44 | 0.94 |
| **Hospital Anxiety and Depression Scale (HADS)** | | | | | | | |
| General anxiety | T1 | 125 | 4.90 | 4.00 | 0.36 | 0.00-18.00 | 0.83 |
| Depression | T1 | 125 | 3.11 | 3.72 | 0.33 | 0.00-17.00 | 0.87 |
| **The Cardiac Anxiety Questionaire (CAQ)** | | | | | | | |
| Avoidance | T1 | 125 | 0.93 | 0.82 | 0.07 | 0.00-3.30 | 0.88 |
| | T4 | 79 | 0.88 | 0.88 | 0.10 | 0.00-3.20 | 0.92 |
| | T5 | 64 | 1.01 | 0.95 | 0.12 | 0.00-3.20 | 0.91 |
| | T6 | 67 | 0.96 | 0.89 | 0.11 | 0.00-2.98 | 0.92 |
| Attention | T1 | 126 | 0.76 | 0.68 | 0.06 | 0.00-2.80 | 0.79 |
| | T4 | 79 | 0.75 | 0.71 | 0.08 | 0.00-3.40 | 0.66 |
| | T5 | 64 | 0.72 | 0.60 | 0.08 | 0.00-2.80 | 0.80 |
| | T6 | 67 | 0.73 | 0.67 | 0.08 | 0.00-2.80 | 0.82 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fear | T1 | 125 | 1.19 | 0.79 | 0.07 | 0.00-3.50 | 0.84 |
| | T4 | 79 | 1.21 | 0.74 | 0.08 | 0.25-3.88 | 0.86 |
| | T5 | 64 | 1.23 | 0.74 | 0.09 | 0.00-3.63 | 0.84 |
| | T6 | 67 | 1.18 | 0.78 | 0.10 | 0.00-3.75 | 0.87 |
| **Self-efficacy expectations (BGCSES)** | T1 | 121 | 8.27 | 1.90 | 0.17 | 0.44-10.00 | 0.96 |
| **Satisfaction with Genetic Counseling (SCS)** | | | | | | | |
| Instrumental (range:3-12) | T1 | 113 | 10.61 | 1.51 | 0.14 | 5.00-12.00 | 0.67 |
| Affective(range:3-12) | T1 | 112 | 11.58 | 1.04 | 0.10 | 5.00-12.00 | 0.81 |
| Procedural (range:3-12) | T1 | 108 | 11.00 | 1.37 | 0.13 | 6.00-12.00 | 0.62 |

## 7.2 Health status in patients at risk of inherited arrhythmias and sudden unexpected death compared to the general population (Paper I)

When investigating health status domains, the results indicated that the total sample (N =127) differed from the general population scores by perceiving their general health to be poorer (controlled for age and gender). When comparing the individual subgroups (genetic risk of LQTS or HCM, diagnosis of LQTS, diagnosis of HCM) to expected general population scores, the patients at genetic risk and patients with a clinical diagnosis of HCM had lower general health scores. In addition the latter group had poorer perceived health related to physical functioning, role physical, vitality and role emotional domains. Comparing the subgroups to each other further supported that patients with a clinical diagnosis of HCM were the most vulnerable group in physical health domains. In general, employment, higher education and being referred to genetic counseling through a family member were associated with better scores on the health status domains.

## 7.3 General anxiety, depression and physical health in relation to symptoms of heart-focused anxiety- a cross sectional study among patients living with the risk of serious arrhythmias and sudden cardiac death (Paper II)

Assessing general anxiety and depression showed that 24.6 % of the patients had scores above cut-off for anxiety and 13.5 % for depression. Overall the patients included in the study (n = 126) reported significantly higher levels of general anxiety compared to expected scores of the general population, but there were no significant differences in depression levels. There were also no significant differences between having a diagnosis of LQTS or HCM, and being at genetic risk of LQTS or HCM,

with regards to levels of general anxiety and depression. Moreover, physical health did not differ significantly from expected scores. However, the subgroup of patients with clinical diagnosis of LQTS or HCM (n = 31) showed poorer physical health as compared to expected scores, whereas patients at genetic risk (n = 89) scored better on physical health as compared to expected scores.

When comparing the patients with familial LQTS to patients with familial HCM, there were no significant differences with regard to the level of general anxiety and depression, whereas poorer physical health and higher scores of heart-focused anxiety (avoidance, attention, fear) were found in the latter group.

When investigating the role of heart-focused anxiety (cardio-protective avoidance, heart-focused attention and fear about heart sensations), the following was found; higher avoidance and fear scores were independently related to higher scores of general anxiety, depression, and lower scores of physical health beyond relevant covariates (age, gender, having children, diagnosis of LQTS or HCM, and recent cardiac death in the family). A recent cardiac death in the family made a significant contribution to the final models predicting higher levels of general anxiety and depression.

## 7.4 Predictors of heart-focused anxiety in patients undergoing genetic investigation and counseling of Long QT syndrome or Hypertrophic cardiomyopathy: A one year follow-up (Paper III)

Investigating heart-focused anxiety over a time period of up to one year showed that scores for avoidance, attention and fear were overall higher in patients with a clinical diagnosis of LQTS or HCM as compared to patients at genetic risk. With exception, at four weeks after genetic counseling (T4) avoidance and fear scores were not significantly different across groups and at six months after genetic counseling (T5) there was no significant difference in attention scores.

Results from mixed linear modelling showed that predisposing factors of heart-focused anxiety were a close relative's sudden cardiac death (predicting higher attention and fear levels), uncertainty whether other relatives previously had undergone genetic testing (predicting higher levels of attention). Factors of prognostic importance for heart-focused anxiety were poorer perceived general health (predicting higher avoidance, attention, and fear levels), higher levels of self-efficacy expectations (predicting lower fear levels) and procedural satisfaction with genetic counseling (predicting lower levels of avoidance and attention). In addition female gender predicted higher levels of fear and receiving a mutation positive test result predicted a higher avoidance level at 6 months after genetic counseling (T5).

# 8. Discussion

## 8.1 Summary of findings

The overall aim of this study was to obtain more knowledge about the health status, levels of general anxiety and depression, and symptoms of heart-focused anxiety in individuals receiving genetic investigation and counseling because of familial LQTS or HCM. This study is the first in Norway investigating, by means of validated and standardized patient-reported outcome measures, the health status, levels of general anxiety and depression levels in the patients receiving genetic counseling for LQTS or HCM. To the best of our knowledge it is also the very first to investigate the role of heart-focused anxiety in relation to general anxiety, depression and physical health, and exploring prospectively predictors of heart-focused anxiety among these individuals who are living with the risk of serious arrhythmias and sudden cardiac death.

Compared to expected scores of the general population the total group of patients had poorer general health and higher levels of general anxiety. Patients with a clinical diagnosis of HCM were especially vulnerable in both physical and mental health domains. There were no significant differences between groups (patients at genetic risk vs. patients with diagnosis; familial LQTS vs. familial HCM) in terms of levels of general anxiety and depression. Especially two distinct symptoms of heart-focused anxiety were related to general anxiety, depression and physical health, namely avoidance and fear. By assessing heart-focused anxiety in patients with a clinical diagnosis as compared to patients at genetic risk, it was found that patients with a clinical diagnosis overall had significantly higher scores of avoidance, attention and fear. However, predisposing factors for heart-focused anxiety over time were a close

relative's sudden cardiac death and uncertainty whether other relatives previously had undergone genetic testing. Other variables of prognostic significance for heart-focused anxiety over time were perceived general health, self-efficacy expectations and procedural satisfaction with genetic counseling.

The following sections will consider some methodological issues and discuss the main findings of the study.

## 8.2 Methodological issues

The present study has several strengths such as the one-year follow up time, the inclusion of consecutive patients at three University hospitals in Norway within a specified time period, and the use of standardized and validated patient-reported outcome measures. However, there are also some weaknesses that need to be addressed pertaining to the study designs, sample and patient-reported outcomes. The strength and weaknesses will be discussed further in the following sections.

### 8.2.1 Study Designs

In order to reach the specific aims of the study several non-experimental designs were implemented; a cross-sectional design, a comparative design, and a prospective design.

*The cross-sectional design*

A cross-sectional design was included as the first step in the present prospective study, thus the socio-demographic, clinical variables, and patient-reported outcomes

were defined at baseline. Strengths of cross-sectional designs pertain to that they are fast, inexpensive and there is no loss to follow-up (Hulley et al., 2007). For descriptive purposes a cross-sectional design is adequate and the design can reveal cross-sectional associations, however a limitation of the design was that it gave only a snap-shot picture of the patient's health status, general anxiety, and depression levels as they were 2-4 weeks before the genetic counseling session (paper I and II). Limitations in drawing conclusions about causality and direction of relationships between the independent and dependent variables therefore exist.

*The comparative design*

The comparison of health status, general anxiety, and depression scores in the sample with expected scores of the general population was a clear strength of the study, since assessing symptoms based on cut-off points may have little clinical significance, when a context for understanding the findings is not provided (Polit & Beck, 2008). Confounding variables may be a weakness in a comparative design. The comparison between health status in the samples and expected scores of the general population were controlled for age and gender, and the comparison of general anxiety and depression to expected scores of the general population were controlled for age, gender, education level, and smoking habits. These variables were therefore eliminated as confounding variables. In comparing the different groups the influences of confounding variables were not controlled for, thus these results must be interpreted with extra caution.

*The prospective design*

We were fortunate to have the possibility to follow-up patients up to one year after genetic counseling. Prospective designs are used for assessing incidence, and are well suited for investigating potential causes for a condition or an outcome (Hulley et al.,

2007). Thus, it was well suited for investigating predictors of heart-focused anxiety. There are several strengths of using a prospective design. First of all it establishes the time sequence of the variables. Second it prevents predictors from being influenced by the outcome itself, and finally measuring variables prospectively will give a more accurate and complete result, as compared to measuring variables retrospectively. This was especially important in the present study, as predictors such as perceived general health, self-efficacy expectations, and satisfaction may be difficult for the patient to remember after some time. The general weaknesses of the design pertain to the challenges of making causal inferences and controlling confounding variables (Polit & Beck, 2008). In addition the design is time-consuming, costly, and inefficient in studying rare outcomes. However, the design may be appropriate studying an outcome such as heart-focused anxiety among patients that are living with the risk of serious arrhythmias and sudden cardiac death, as compared to studying heart-focused anxiety in for example a normal population.

### 8.2.2 Sample

*Choosing the study subjects*

To ensure that the findings in a study accurately represent the population in interest, the selection of study subjects is very important (Hulley et al., 2007). At the time when this study was initiated clinical genetic investigation of familial cardiac disorders had just started in Norway. To obtain more knowledge about the patients, the aim of the study was to investigate the health status, levels of general anxiety and depression, and symptoms of heart-focused anxiety in individuals that were undergoing genetic investigation and counseling for LQTS or HCM. The patients were family members and other appropriate relatives subsequently following the identification of a LQTS or HCM- causative mutation in an index case or individuals in whom a cardiologist had established or suspected a clinical diagnosis of LQTS or

HCM. This heterogeneous study sample was chosen based on expectations that the entities by themselves would not produce big enough sample sizes, thus a pragmatic approach was needed. A pragmatic approach could be justified partly because, the two entities, LQTS and HCM share a lot of common features, especially with regard to the risk of arrhythmia, syncope, and sudden cardiac death, and how they are managed in the genetic counseling setting, and partly because both patients with a clinical diagnosis as well as their relatives at genetic risk may manifest serious symptoms. We therefore investigated a sample of patients fulfilling the inclusion criteria in their natural contact with the genetic outpatient clinic. Every accessible person who met the entry criteria in three different regional tertiary hospitals was consecutively included to minimize volunteerism and other selection biases (Hulley et al., 2007).

*Number of study subjects*

A priori computations had been made regarding a needed sample size of 250 for detecting small and moderate changes, and for comparisons within the group and between groups based on two-tailed tests, alpha-level of 0.05, and power of 0.80. However, despite that several steps were taken to increase the response rate, such as pre-stamped, pre-addressed return envelopes, and one repeated contact attempt by post asking non-responding patients to participate in the study, it was not possible to reach this sample-size, partly due to the non-responders, but also that there were not enough eligible participants within the time frame of the study. The limited number of patients attending genetic counseling for familial LQTS or familial HCM made it especially difficult to achieve sufficient sample sizes according to the previous power estimates of the study. This may also explain some of the unexpected insignificant results in the smaller subgroups.

*Non-response and loss to follow-up*

In achieving a representative sample a particular concern is non –response. The level of non-response may compromise the generalizability of the study (Hulley et al., 2007). Of 173 eligible patients, one hundred and twenty-seven patients were willing to participate (73.4 %), which may be considered a satisfactory response rate. However a non-response rate of 26.6% at baseline may influence the results. We do not have any information about this group as we were not allowed to register information on the decliners. For example, in case of an under-representation of individuals with a "severe family history" this may result in weaker observed effects on, for example, psychological variables.

Furthermore, on the course of the study patients dropped out, which may cause attrition bias (Polit & Beck, 2008). The explanation for how the n can increase from one point to the next (as from T5 to T6) is that some participants were non-responders at T5, but responded at T6. At one year after genetic counseling, 58 individuals had dropped out. However, there were no significant differences between the study sample and these drop-outs on any of the variables in the prospective study (paper III, table 1). The fact that not all participants completed all time points could potentially also cause problems for the statistical analysis. In order to meet this weakness the method of Mixed Linear Method was used. It is designed for tracking changes over time, even with missing data at certain questionnaire time points. The method uses all available data and can account for correlations between repeated measurements on the same subjects and has flexibility to model time effects.

*Patients' subcategories*

At the time when the study started the patients attending genetic counseling for familial cardiac disorders mainly consisted of LQTS or HCM patients and their at-risk relatives. We therefore included patients with a clinical diagnosis as well as

unaffected patients with a presumed genetic risk. However, these subcategories may be regarded as very different. We could not fully address these differences in the present study, thus this could introduce bias, although we did subgroup analyses in all of the papers. By considering patients at family risk, patients with a clinical diagnosis of LQTS, and patients with a clinical diagnosis of HCM separately in the comparison to expected scores of the general population, it was ensured that patients similar according to clinical status were compared to the expected scores. It was however a limitation that the groups were so different in size, when comparing them to each other.

More patients with familial LQTS were included in the study as compared to patients with familial HCM, despite that HCM is a more prevalent disease. The reason for this may be that the possibility of genetic testing for LQTS started in 2001, whereas molecular genetics for HCM was only possible from 2004, thus the possibilities of genetic investigation may therefore not have been widely known among HCM patients and their physicians in the study period. LQTS molecular testing may also be perceived as more important for diagnostics, since patients with normal ECGs and no clinical manifestations still may be at risk.

### 8.2.3 The patient-reported outcomes

The patient-reported outcome measures were selected based on the aims of the present study, previous research, clinical experience, and the patient-reported outcome literature. Main strengths of the study were the use of well-established, standardized, validated questionnaires. An exception is the The Bergen Genetic Counseling Self-efficacy Scale (BGCSES), which has not been validated, but has been constructed based on Banduras guidelines (see section 6.4.4). The instrument has shown high reliability in previous studies (Bjorvatn et al., 2008; Bjorvatn et al., 2009). A generic questionnaire measuring patient general health and wellbeing, as

well as questionnaires that measured specific dimensions to a greater extent were selected as patient-reported outcomes. The advantage of using generic instruments is that they can be used in general population trials or across patients with different disease conditions (Fayers & Machin, 2007). For example, SF-36 is not age, disease or treatment specific, and has therefore several advantages. It is applicable to patients with more than one disease, and it can be used to compare patient-groups who suffer from different diseases (Loge et al., 1998). It is therefore appropriate in the present study where the sample consists of patients presumed to be at genetic risk of LQTS or HCM, as well as patients who already have a diagnosis of LQTS or HCM due to clinical findings, and of two reference populations from which expected scores of the general population were calculated.

The advantages of using a dimension-specific instrument pertain to documenting dimensions that are of special interest or particularly important to the patient group in question (Fayers & Machin, 2007). For example, it is likely that anxiety among patients with a suspected risk of heart conditions will be related at some level to the functioning and sensations of the heart. A dimension-specific instrument like CAQ would capture this, whereas a generic questionnaire would be inadequate. A negative consequence of including both generic and dimension-specific instruments in the present study was that the questionnaire package took a long time to complete for the patients. This may have led to missing items on some of the questions. Missing substitution was performed according to standard procedures for the SF-36 questionnaire (Medical Outcomes Trust, 1994). For the remaining questionnaires mean imputation were used, where over half of the questions were filled in (Fayers & Sprangers, 2002).

The questionnaires have shown good reliability in previous studies. In the present study, Cronbach's alpha (Table 7.2) was in general good, with exception of the

subscale of procedural satisfaction. This may be due to the few items of this scale (Fayers & Machin, 2007).

In the following sections, central findings regarding the patient-reported outcomes, impact of socio-demographic and clinical variables, the influence of having a family history of sudden cardiac death, and the role of heart-focused anxiety in relation to patient-reported outcomes will be discussed. Furthermore, this discussion will explore possible explanations for differences in patient-reported heart-focused anxiety up to one year after genetic counseling, and discuss some emerging issues relating to the contents and optimal dimensions of health care services in the future.

## 8.3 Patient- reported health status, levels of general anxiety and depression, and symptoms of heart-focused anxiety

*Health status*

The present study demonstrates reduced health status in the SF-36 domain of general health in individuals receiving genetic investigation and counseling because of familial long QT syndrome (LQTS) or familial hypertrophic cardiomyopathy (HCM). Approximately 75 % of these individuals were termed “patients at genetic risk” because they were family members and other appropriate relatives subsequently following the identification of a LQTS or HCM- causative mutation in an index case, and thus without a clinical diagnosis. In line with that the patients at genetic risk currently were clinically unaffected by LQTS or HCM, these patients had better health status scores on physical functioning and the bodily pain domains compared to

the expected scores of general population. However, by their own the patients at genetic risk also had markedly reduced general health scores.

In our study general health is defined as current health, resistance to illness, and health outlook, which can be considered to belong to one overall dimension of perceived health (Bjorner & Kristensen, 1999). Perceived health allows the patients to weigh together different aspects of their health in an overall score, thus the aspects that the patient deem relevant is emphasized (Fayers & Sprangers, 2002). Living with the risk of serious arrhythmias and sudden cardiac death implies a probability for something adverse can happen in the future. LQTS and HCM are autosomal dominant disorders, which mean children, siblings and parents of a mutation carrier have a 50 percent risk of also being affected, thus they are also living with risk of serious cardiac symptoms. The penetrance (likelihood for actually developing the disease) is however varying, which leads to uncertainty of ever experiencing clinical symptoms of the disorder. Living with this health threat may cause the patients to feel vulnerable. In turn, this perceived vulnerability may result in poorer perceived general health.

In contrast to the poorer perceived general health, physical functioning, role limitation-physical, bodily pain, vitality, social functioning, role limitation-emotional, and mental health domains were not significantly different as compared to expected scores in the general population. However, all health status domains were influenced by clinical variables as well as socio-demographic variables.

With regard to the adult population affected with LQTS or HCM, health status has previously only been measured with well-established, standardized and validated measures in HCM patients, indicating that patients with a clinical diagnosis of HCM

have major limitations on both physical and mental health domains (Cox et al., 1997). Although many patients with HCM can be asymptomatic, clinical manifestations such as dyspnea, dizziness, syncope and angina are common (Stroumpoulis et al., 2010). The presence and severity of symptoms may most likely be the reason for reduced scores in physical and role physical activities as well as the lower scores on the vitality domain. The HCM patients in the present study were not significantly different from the general population on levels of bodily pain, social functioning, or mental health. However they did have poorer perceived general health.

In contrast to the limitations the HCM patients experienced, the scores of the LQTS patients were not significantly different than those of the general population on any of the health status domains. However, the group may have been too small to detect significant differences, and it is worth to note that the scores on several of the health status domains were moderately lower also among the LQTS patients. This was especially pertaining to general health and vitality, where the differences in scores may be an indication of poorer perceived health. Being a generic instrument, measuring patients general health and wellbeing, the SF-36 may not completely capture the health problems of LQTS patients, since qualitative research clearly have found evidence of daily limitations related to periodic feelings of extreme fatigue, exhaustion, palpitations and headaches in this patient group (Andersen et al., 2008).

Variables like gender, age and education status were expected to have an influence on health status since they are common confounders in health research using patient-reported outcome measures (Polit & Beck, 2008). Health status was therefore investigated in relation to socio-demographic variables. As to gender differences previous research has shown gender differences in anxiety disorders and symptoms (Lewinsohn et al., 1998). We found that female gender was related to lower scores on domains that measure well-being, such as bodily pain, vitality, and mental health.

Patients that had children also scored lower on mental health. This is understandable, since much of the literature has identified raised anxiety levels in parents having children at risk of these disorders (Hendriks et al., 2005b; Hendriks et al., 2005a). Increasing age had an impact on physical health. Lower education level indicated poorer health status, as can also be found in general population samples (Loge & Kaasa, 1998). Physician referral to genetic counseling was related to poorer health status on all health domains. Referral from a physician may therefore indicate that the patient more likely was clinically affected.

*General anxiety and depression*

While there were large differences in health status according to clinical status, no differences were found in terms of general anxiety and depression between patients at genetic risk and patients with a clinical diagnosis. The anxiety levels were elevated compared to the general population controlled for gender, age, education level, and smoking status. The prevalence of general anxiety (scores over >8, HADS) in the patients before genetic counseling was 25%, which is quite high in comparison to the prevalence among Dutch HCM mutation carriers (Christiaans et al., 2009b), and the prevalence in general population samples (13-18%). It was however comparable to the proportion of patients anxious before attending genetic counseling for hereditary cancer (Bjorvatn et al., 2008). Receiving the invitation to participate in the study and the scheduled genetic counseling session may have actualized anxiety in some of the individuals. However, it cannot be ruled out that living with this health threat in itself may have an impact on levels of general anxiety.

*Heart-focused anxiety*

In contrast to that there were no differences in general anxiety between any of the groups, patients with a clinical diagnosis had significant higher levels of heart-

focused anxiety than the patients at genetic risk, and patients receiving genetic counseling because of familial HCM had higher levels of heart-focused anxiety compared to patients receiving genetic counseling because of familial LQTS. In terms of explaining possible reasons for a relationship between greater heart defect complexity and higher levels of heart-focused anxiety, Ong and colleagues suggested that patients with greater defect complexity may be more symptomatic, have greater functional impairments, and have a history of more medical interventions that may trigger heart-focused anxiety (2011). This may also be the case for patients with clinical diagnoses, and especially the HCM patients. Therefore, higher heart-focused anxiety among patients affected clinically, especially with HCM may most likely be due to that they experience more symptoms, functional impairments, and contact with health care services that can trigger fear for adverse outcomes.

In summary, patients with a clinical diagnosis had poorer physical health and higher levels of heart-focused anxiety, whereas patients at genetic risk scored better on these domains. Common for the patients at genetic risk of LQTS or HCM and patients with a diagnosis of LQTS or HCM, were poorer perceived general health and higher levels of general anxiety.

### 8.3.1 The impact of having a family history of sudden cardiac death

One consequence of living in a family with a familial cardiac disorder is the possibility that a relative suffers a cardiac arrest and dies unexpectedly. Fifty–seven individuals (45%) had experienced sudden cardiac death in a relative. Thirty-five of these individuals (28%) had experienced sudden cardiac death in a close relative (first or second degree relative), and 25 individuals (20%) had experienced that a relative had died of a cardiac arrest less than a year ago.

In the present study it was found that having a family history of sudden cardiac death impacted on several of the patient- reported outcomes. Counter intuitively, when investigating socio- demographic variables relationship to health status domains, it was found that patients that had reported a sudden cardiac death event among any of their relatives at any point in time, had higher scores on the health domain of bodily pain (less bodily pain). This result may have been confounded, but it may also be evidence of a response shift. Experiencing a relative's death event may be very dramatic, and it is possible that an event like that can change a person's self-evaluation as to having less bodily pain or no bodily pain, as opposed to more (Schwartz et al., 2007). The better physical health scores than expected among the patients at genetic risk in the present study may also be due to similar mechanisms.

Psychological processes may be involved, since we found that the experience of a recent cardiac death of a relative was associated with higher levels of general anxiety and depression. Patients may also not relate a sudden cardiac death event in the family so negatively to general bodily pain as they would to specific perceived heart symptoms, which more likely will represent a greater extent health threat. The latter alternative was supported by the fact that a sudden cardiac death event in a close relative (first or second degree relative) predicted higher levels of heart-focused attention and fear about heart sensations up to one year after genetic counseling.

### 8.3.2 The role of heart-focused anxiety

The fear of cardiac-related events and sensations may potentially also in itself contribute to higher levels of general anxiety and influence heart-related illness (Eifert et al., 2000b). For example, in a study of patients undergoing cardiac surgery, Hoyer et al.,(2008) found that heart-focused anxiety was significantly correlated with higher levels of anxiety and depression and lower health –related quality of life, and Zvolensky et al., (2003) found that heart-focused attention and fear about heart sensations predicted self-reported chest pain intensity among patients with coronary

disease. In the present study two distinct symptoms of heart-focused anxiety, the degree of cardio-protective avoidance and fear about heart sensations, could explain a considerate part of the higher levels of general anxiety and depression in the patients, in addition to patients lower scores on physical health. First, cardio-protective avoidance is a recommendation to avoid aversive events in patients with the risk of serious arrhythmias. Knowing that activity actually can trigger events may therefore in itself cause patients to avoid all kinds of activity and fear any heart sensation, which would impact on physical health as well as on general anxiety and depression. Secondly, both avoidance and fear may be due to that the patients actually have poorer health. It is therefore difficult to interpret whether avoidance and fears in relationship to physical health is due to medical recommendations for patients that are affected, or that the avoidance and fear is due to poorer health. However, high levels of avoidance and fear may be considered as important risk factors for higher levels of general anxiety and depression, as well as poorer health functioning.

### 8.3.3 Explanations for differences in heart-focused anxiety up to one year after genetic counseling

Research on patients undergoing genetic counseling has so far mostly focused on the possible negative effects of genetic testing. Complementary to this, the present findings show that knowing whether other relatives had undergone genetic testing, higher self-efficacy expectations, and higher levels of procedural satisfaction after counseling actually reduced fearful responses to cardiac-related stimuli and sensations over time. This indicates less heart-focused anxiety among patients that knew there would be possibilities of genetic testing, that thought they would cope with challenges connected to the genetic counseling, and that were more satisfied with waiting time and administrative tasks around the counseling session.

In addition the present findings underline the importance of the patients' perspective of health. Interestingly, poorer perceived general health as measured before genetic counseling was an important predictor for heart-focused anxiety, as it predicted avoidance, attention, as well as fears up to one year after genetic counseling.

Perceived general health has previously been shown to influence clinical outcome, as well as being a powerful predictor of mortality and morbidity (Fayers & Sprangers, 2002). In a study reporting predictors of 10-year survival in women after acute myocardial infarction, those that perceived poorer general health had a two times higher risk of dying (Norekval et al., 2010), thus it may be a variable of particular interest to study in future studies in the present patient group, since they have poorer perceived general health as compared to the general population.

## 8.4 Emerging issues related to genetic investigation and counseling now and in the future

The rapidly developing gene technology has made it possible to identify individuals with an increased risk for diseases. This development will likely have substantially impact on future treatment and care. With an increasing number of individuals seeking genetic investigation for familial cardiac disorders, finding ways to maintain a high health functioning and emotional wellbeing among the patients are essential to be able to argue for increased use of genetic testing in cardio-genetic care.

Today diagnostic genetic testing in Norway can be performed without prior genetic counseling, whereas patients undergoing predictive genetic testing are protected by the law and are entitled to genetic counseling before, during, and after the testing (Act of biotechnology, 2003, appendix). Patients clinically affected by disease should also be entitled to genetic counseling before genetic investigation, because finding a mutation has further consequences than just confirming the diagnosis in that individual. For example, higher levels of heart-focused anxiety were found in the patients with a diagnosis compared to patients at genetic risk. The genetic counseling provides a venue for addressing heart-focused anxiety. Further, current practice of genetic counseling includes information and performance of cascade genetic testing of at-risk relatives. As discussed in Hamang et al., (2009) the current Act of Biotechnology does not automatically allow communication of genetic information to persons other than the patient. This means that the patients themselves have to be instrumental in informing other relatives of genetic test results and risks. Index patients with clinical diagnosis may therefore have even greater need for genetic counseling, because they have to inform others.

Common for LQTS and HCM patient groups, before genetic investigation and counseling, were a higher general anxiety level compared to what is expected in the general population beyond reported health status or whether the patients were affected or unaffected with the familial disorder. The higher general anxiety level may have been due to the upcoming genetic counseling session. However a more likely explanation may be that general anxiety is an important determinant for undergoing genetic testing in the first place, since previous research has shown decreased levels of general anxiety over time in for example patients undergoing predictive genetic testing for familial LQTS (Hendriks et al., 2008). In the present study it was shown that the patients had high satisfaction with genetic counseling, and that satisfaction with the procedural parts of genetic counseling decreased heart-focused anxiety levels. The continuation of genetic counseling is therefore necessary in the future.

Following the protocol of predictive genetic testing, most of the patients that were offered genetic testing, underwent testing. This is clearly different from our experience in cancer counseling, where more patients decline genetic investigation after counseling. There may be several explanations for this. It may for example be due to that the protocol of predictive testing of patients is different in cardiac disorders compared to cancer, since the decision to undergo testing is not postponed, because of the immediate risk of symptoms and sudden death, the greater risk in young age, and that preventive measures are available. Alternatively, it may also be due to that there are greater detection rates in the genetic testing of cardiac disorders, and that the result of the testing has more consequences in terms of preventive measures. Even though there are positive aspects of finding a mutation, like surveillance and other medical strategies to reduce risk of sudden cardiac death, the patients often have to wait a long time for a heart control. A more team-based approach between the genetic counselor and cardiologist may be beneficial for the patient to cope with a positive genetic test result.

The field of medicine has become highly specialized. The application of genetics to cardiology is one example where the care of patients involves medical, psychological, and familial challenges, of which the present health care system may lack expertise and resources to oversee (Patterson, 2009). The purpose of a more team based approach must be to offer the patients and their families an optimal cardiological and genetic examination and follow-up as well as increasing knowledge among patients, their families, and the health care personnel.

The clinical guidelines emphasize the importance of genetic testing in LQTS families and the usefulness in families with HCM (Zipes et al., 2006) in the prevention of serious arrhythmias and sudden cardiac death. The clinical guidelines should also include the importance of genetic counseling as stated in the recent expert consensus recommendations of genetic testing for the channelopathies and cardiomyopathies (Ackerman et al., 2011).

# 9. Conclusions

The studies included in this thesis show that the use of patient-reported outcome measures allows for better understanding, not only of the effect of the conditions themselves, but also of some of the effects of living with this health threat, and finally of how outcome is influenced over the course of the study. The three papers included in the present thesis elaborate on these findings. The following conclusions were made:

Paper I:

In a cross-sectional design it was found that living with the risk of serious arrhythmias and sudden cardiac death most likely affects the perceived general health in patients receiving genetic counseling for familial LQTS or familial HCM. However the patients' scores on the other health status domains were not impaired compared to what is expected in the general population.

There were however significant differences of the effect of the conditions themselves. Patients with a clinical diagnosis of HCM reported more impairment compared to the general population in physical functioning, role physical, and vitality domains, whereas patients with family risk of LQTS or HCM reported better physical functioning and less bodily pain.

Several socio-demographic variables and clinical variables were related to better perceived health status, notably employment, higher education level and referral to genetic counseling by a family member. Better self-reported physical functioning and

general health were in addition predicted by that the patients were referred for familial LQTS as opposed to familial HCM, supporting that the HCM patients were the most vulnerable in physical health domains.

Paper II:

Before receiving genetic counseling, the individuals with familial LQTS and familial HCM had higher levels of general anxiety than expected in the general population, whereas their level of depression and overall physical health were no different.

Comparisons between familial LQTS and familial HCM revealed no difference between the groups with regard to general anxiety and depression, whereas heart-focused anxiety was higher and physical health was poorer in the familial HCM group.

Both heart-focused avoidance and fear about heart sensations had important roles in determining patients' levels of general anxiety, depression and physical health. To what extent these individuals experienced heart-focused avoidance and fear about heart sensations, their reporting of general anxiety, depression, and physical health were related to varying degrees by these distinct symptoms of heart-focused anxiety. In addition, having a clinical diagnosis was of importance for their physical health, whereas a recent SCD in the family was related to higher levels of general anxiety and depression, regardless of disease status.

Paper III

In a prospective design the three distinct symptoms of heart-focused anxiety (avoidance, attention, fear) were overall higher in patients with a clinical diagnosis of LQTS or HCM as compared to patients at genetic risk of LQTS or HCM, indicating that patients affected with a familial cardiac disorder have higher heart-focused anxiety.

Predisposing factors for higher levels of heart-focused anxiety over time were a family history of sudden cardiac death in a close relative and uncertainty whether other relatives had undergone genetic testing. However, satisfaction with the procedural parts of genetic counseling was predictive of decreased levels of heart-focused anxiety. The resources of greatest prognostic importance may be the way individuals perceive their general health and their self-efficacy expectations.

The present findings indicate that patients undergoing genetic investigation and counseling for familial LQTS or familial HCM are vulnerable in both health-related and psychological domains before genetic counseling, and may benefit from a closer collaboration between the genetic counselor and the cardiologist addressing their experience of cardiac symptoms to a greater extent.

# 10. Clinical implications

For the continuation of developing genetic counseling for these patients it is important to increase the understanding of the possibilities for improving quality of care. The patient-reported outcomes in this study allows for a better understanding of how this can be achieved.

As stated previously in this thesis the main aim of genetic counseling is to help people to understand and adapt to the medical, psychological, and familial implications of genetic contribution to disease. The present study showed that one implication of living with the risk of serious arrhythmias and sudden cardiac death, in individuals with familial LQTS or familial HCM, was a poorer perceived health and a higher level of general anxiety than that of the general population. *How may genetic investigation and counseling improve perceived general health and anxiety levels?*

Undergoing genetic investigation may in itself influence health perception and levels of general anxiety, for example by reassuring patients when they test negative for the family mutation (Aatre & Day, 2011), or by providing access to better follow-up and that feelings of uncertainty is removed for persons testing positive for the family mutation. Patients who already have a clinical diagnosis of LQTS or HCM may get more information about the etiology of the disorder, and learn more about the consequences for other relatives (Skrzynia, Demo, & Baxter, 2009).

Individualizing the genetic counseling session to an even greater extent may also be a way to go. Today the protocol for pre-test counseling session of patients with familial

LQTS and familial HCM is more or less the same. Although the present study showed that these patient groups were similar with regards to general anxiety levels, the patients with a diagnosis of HCM demonstrated limitations in physical health domains compared to the general population, and were identified as the most vulnerable group with regards to health functioning. This indicates that the genetic counseling should adapt to this, using a more individual based approach to families with HCM, as they may have more concerns of health limitations, whereas LQTS patients may have other needs in their management of potential health threat.

The genetic counselor may also try to educate the patients about their health and normalize emotions patients may have in relation to living with the risk. A study among individuals with panic disorder showed that individuals who perceived their health as poorer were more likely to experience anxiety, anger, depression and frustration (Gregor et al., 2005). This may indicate that by addressing general health perception the genetic counselor may also become aware of unresolved emotions of the patient. In the present sample poorer general health also predicted higher scores of cardio-protective behavior, heart-focused attention, and fear about heart sensations, which underlines the importance of addressing this patient-reported outcome.

Before the patient is undergoing genetic investigation and counseling, heart-focused anxiety should be assessed. Being important in determining levels of general anxiety and depression, and physical health, this assessment will give the genetic counselor access to important information. Healthy persons that are heart-anxious are more likely to report panic and other anxiety disorders, more hypochondrial beliefs, physical symptoms, obsessive-compulsive concerns and negative affect (Eifert et al., 1996). Our findings indicate that heart-focused anxiety may be a substantial problem among patients receiving genetic counseling for familial LQTS or familial HCM, most prevalent among clinically affected patients.  Intervention aimed at heart-

focused anxiety may therefore increase health functioning and decrease general anxiety both in patients with and without cardiac disease (Eifert et al., 2000a; Eifert, 2000b). Genetic investigation and counseling may be targeted as such intervention.

# 11. Implications for further research

This study indicates that there are differences as well as similarities between HCM and LQTS patient groups.

Big differences were found in health status. LQTS patients' health status should be further investigated in bigger samples, and possibly with other patient-reported outcome measures that more can reflect the health issues in this population.

In contrast to the differences in health status it was found that knowledge of a heightened genetic risk for serious arrhythmias and sudden cardiac death most likely is associated with anxiety pathology, regardless of disease status or familial LQTS or familial HCM. Since previous research has shown that general anxiety may decrease over time in patients at risk of familial LQTS (Hendriks et al., 2008), the role of genetic counseling should be investigated.

Further, we have shown that specific anxiety for heart events may contribute to raise levels of general anxiety and depression. In addition to that heart-focused anxiety is related to poorer physical health. However, it still needs to be investigated what other variables may influence general anxiety in these patients.

In addition, it is necessary to explore further if the high general anxiety before genetic counseling is due to the upcoming counseling session, or if the individuals by themselves are anxious because of living with this health threat and uncertainty.

In contrast to more general anxiety and distress levels that can be caused by many factors, heart-focused anxiety is the specific fear of cardiac-related stimuli and sensations because of their perceived negative consequences. Fearful responding to symptoms and information about risk may also have a profound negative effect on social and occupational life functioning (Eifert, 2000b), and this should be further explored in HCM and LQTS patients.

The importance of understanding the association between perceived health and emotional vulnerability processes such as heart-focused anxiety has been pointed out, and suggests the need for further work investigating this cognitive variable as a possible risk factor for developing such problems (Yartz et al., 2005). Even more important in this patient group is the possible relationship between perceived health, heart-focused anxiety, and mortality.

Finally, to what extent the present patient-reported outcomes may be different in individuals undergoing genetic investigation and counseling because of familial LQTS or familial HCM, from patients with other genetic diseases, or in healthy persons, should be further explored in future research.

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# Original papers