Clinical genetic care in diseases predisposing to sudden cardiac death
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Summary, conclusions and future plans
Summary

The scope of this thesis is on the practical consequences, for care-givers and patients, of recent developments in the scientific insights in heritable causes for cardiac diseases predisposing to sudden death at young age. The molecular background of these, primarily autosomal dominantly inherited, disorders was (partly) clarified in the last decade, which facilitated cascade screening by DNA-testing in many affected families. In the Introduction (chapter 1) an overview of diseases associated with sudden cardiac death is given and definitions of genetic counselling and guidelines for testing, in general and applied to cardiogenetics, are presented. These diseases can be divided into two main categories, the (relatively rare) primary cardiac arrhythmias and the (more common) cardiomyopathies. Prophylactic treatment to reduce the risk of sudden death is possible in carriers of the predisposition to these diseases. In the Netherlands, cascade screening is currently mainly performed in families affected with the Long QT Syndrome (LQTS), the Brugada syndrome (BS), familial Cathecholaminergic induced Polymorphic Ventricular Tachycardia (CPVT) and Hypertrophic CardioMyopathy (HCM) and recently with Arrhythmogenic Right Ventricular Dysplasia (ARVD).

The academic outpatient cardiogenetic clinic in the AMC, primarily set up to facilitate molecular genetic research regarding these disorders, offered important opportunities to develop and investigate various aspects of care for this new category of patients in the clinical genetic practice. The outpatient cardiogenetic clinics in Alkmaar (MCA), Utrecht (UMC) and Groningen (UMCG) were involved in this research as well, as were the Dutch cardiologists and clinical geneticists and the molecular diagnostic labs. Research involved organisational aspects, under which the readiness of cardiologists for clinical genetic tasks and the preferred (future) cooperation of clinical geneticist and cardiologists in cardiogenetics (Part I). Also the implications for genetic counselling, particularly in predictive testing, and the opportunities for, and potential difficulties with, population screening could be investigated, including the psychological consequences of revealing the inclination for diseases predisposing to sudden death in adults as well as in children (Part II). The most efficient way of molecular screening in index patients with one of the primary arrhythmias, the LQTS, a genetically heterogeneous disease, like all discussed diseases predisposing to sudden death, was also evaluated (Part III).

Part I Multidisciplinary organisation of care

In chapter 2 a survey is presented that assessed the current Dutch cardiologists’ experience with genetic aspects of HCM, their self-reported genetic knowledge, and their genetic skills in general and aimed at HCM (response 33%, 197 cardiologists, data sampling in 2000). The median number of HCM-patients in follow up with these cardiologists was 5. Forty-one percent of respondents do not give information about genetics to all their patients. Cardiologists rarely initiate DNA-tests for HCM. Only 38% refer patients to a clinical geneticist for counselling and testing. Self-reported knowledge levels are insufficient, with an average score of 3.3-5.1 on a 0 to 10 scale. Cardiologists having an established working-relationship with a clinical
geneticist report significantly higher levels of knowledge. Clinical guidelines, education and improved collaboration with clinical geneticists are preferred by the majority. We conclude that the reported theoretical and practical knowledge on genetics, in general and applied to HCM, of Dutch cardiologists is insufficient. This results in suboptimal clinical genetic care for HCM patients. Cardiologists realize that they need guidelines, education and closer working relationships with clinical geneticists to increase their knowledge and abilities in cardiogenetics. Therefore we conclude that improvement can be expected in the near future, provided that the desired measurements are offered.

In the year 2005 educational options as well as working relationships have improved, which makes it likely that knowledge and skills of the Dutch cardiologists increased as well, compared to the situation during our investigation.

In chapter 3 preferences of individual Dutch cardiologists’ and clinical geneticists for the future organisation of genetic care in HCM were studied. In view of the increasing demands for genetic counselling and DNA-diagnostics in cardiogenetics, cardiologists’ and clinical geneticists’ roles in the delivery of care may need adjustments. By cross-sectional survey we investigated the preferences of members of both groups for the future allocation of six cardiogenetic responsibilities in counselling and testing, with HCM as a prevalent model disease. The same 197 cardiologists (chapter 2) and 49 clinical geneticists (response rate 82%) responded. In both groups, the majority preferred to perform most tasks in collaboration. ‘Informing HCM-patients about the genetic aspects of their disease’ and ‘requesting DNA-testing in symptomatic patients’ was viewed by 43% and 35% of cardiologists as their sole responsibility however, and 39% and 59% of clinical geneticists did not object. Both groups expressed that ‘discussing the consequences of HCM for offspring’ and ‘discussing the results of DNA-diagnostics’ should be shared, or performed by clinical geneticists. Both groups considered ‘co-ordination of family screening’ the sole responsibility of clinical geneticists. Opinions on ‘requesting DNA-diagnostics in asymptomatic relatives’ were divided: 86% of clinical geneticists thought it their exclusive responsibility, while 10% of cardiologists thought that both groups could perform this individually and 30% preferred to collaborate here. The majority of clinical geneticists, like the cardiologists, desired measures to improve their knowledge and skills regarding cardiogenetics. Because cardiologists and clinical geneticists prefer to share rather than divide most cardiogenetic responsibilities in caring for HCM-patients, capacity problems in both groups can be awaited. To increase this capacity could be a solution, but this will take time. To safeguard current professional standards in genetic counselling and testing, ongoing deployment of paramedical personnel, cardiogenetic counsellors, might be essential.

**Part II  Genetic counselling and population screening**

Chapter 4 describes the status quo in family and population strategies for screening and counselling for inherited cardiac arrhythmias. Systematic family screening in inherited cardiac arrhythmias has been performed in the Netherlands since 1996, when diagnostic DNA-testing in LQTS and HCM became technically possible. In our multidisciplinary outpatient academic
clinic, an adjusted protocol for genetic counselling, originally developed for predictive testing in Huntington’s disease, is being used. From 1996 until 2003, at this outpatient clinic 1100 individuals, including 842 relatives of index patients, were informed about their risks, and most were tested molecularly and/or clinically for carriership of the disease present in their family. Of 345 relatives who were referred for cardiologic follow-up, 189 are being treated, because of an increased risk of life-threatening arrhythmias.

Evaluation of the psychological and social consequences of family screening for inherited arrhythmias can be performed by using the adapted criteria of Wilson and Jüngner, i.e., from a point of view of Public Health. Preliminary results of psychological research show that parents of children at risk for LQTS show high levels of distress. Many other aspects have to be evaluated yet, making final conclusions about the feasibility of family screening difficult, particularly in HCM, where general risks are smaller and preventive measures more invasive. Clinical guidelines for pre- and post-test counselling are urgently needed as well. Population screening by molecular testing, for instance in athletic preparticipation screening, will become possible in the future and has its own prerequisites for success.

Chapter 5 is a study dating from 2002, using heritable diseases predisposing to sudden cardiac death as examples to describe the trade off between the medical benefits of genetic discoveries and the complex societal side effects accompanying them. Sudden death in the young has an unprecedented emotional impact on all involved. When its cause is suspected or established to be genetic, relatives not only experience the grief of losing their loved one, but also face the psychological, social and medical problems that arise from this knowledge for themselves and their family, including their (future) children. Prevention of sudden death in those identified to be at risk is possible, by change of life style, medication or invasive measures like implantation of pacemakers or internal defbrillators. Although the benefits of such preventive measures seem to outweigh the burden of medical side-effects at this stage, the precise risks of premature death in asymptomatic relatives of a given age and a given genetic status are largely unknown, evoking a dilemma due to the considerable societal side effects. Current knowledge at least estimates prevalences of 1:500 and 1:5000 in the most common sudden death syndromes (HCM and LQTS). Consequently, identification of risk carriers by predictive DNA testing through cascade screening has been actively offered to hundreds of relatives of patient with a proven mutation in one of these genes. Due to limited availability of these tests, no general evidence exists on the ethical, legal, social, and psychological impact of predictive testing in sudden death syndromes, nor on the normative views of the public.

Based on a concise review of the literature on predictive testing, and our expertise with predictive DNA-diagnostics of and research in premature, familiar sudden death, we developed a detailed questionnaire that was used in face to face interviews with both stakeholders (families involved in predictive DNA-testing, and consumer groups) and (medical) professionals. The interviews focused on the justification of offering family based predictive testing (cascade screening), and, if cascade screening was desired, the questions were entailed on the organisation of the predictive testing procedure. Additionally, legal, psychosocial, ethical and societal topics associated with the identification of an increased risk for sudden death were dealt with.
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All interviewees unanimously justified cascade screening for (penetrant) mutations predisposing to sudden cardiac death. They also widely supported the multidisciplinary approach in academic centres. The interviewees differed in their opinions on population strategies dealing with these diseases and the preferred position of general practitioners. In spite of a lack of information on many aspects (medical as well as psychosocial and societal), design of guidelines is desirable, but revision should be guaranteed with accumulating evidence from further studies. Future research is needed to address medical aspects (risks of premature death in asymptomatic mutation carriers including children, compliance to and burden of preventive measures), psychosocial aspects (family dynamics, psychosocial care on demand or imposed under specific circumstances), and ethical aspects (patient autonomy, family rights and responsibilities).

Political issues involve the desired population strategy concerning sudden cardiac death, as well as the still unresolved debate on the unrestricted access to insurances.

For polymorphisms increasing the risk of premature sudden death in triggering circumstances (like the use of certain medications), we advise individually, not family based predictive DNA-testing. These tests might in such cases be offered by the specialists treating these patients.

In chapter 6 we investigated the counselling needs of several client groups, by relating their so-called agenda-topics (list of desired items to discuss during the first session) to background characteristics, to guide the development of tailored care in genetic counselling and testing in cardiogenetics. Genetic counselling and testing for preventable cardiologic disorders predisposing to premature sudden death is a new area of interest of clinical geneticists and cardiologists. Disease-related and counsellee’s characteristics are likely to result in different counselling needs compared to existing, non-cardiologic patient groups requiring this type of care.

We performed a cross-sectional survey among a one year cohort of all eligible counsellees attending the clinical genetics department in the AMC (non-Cg group; 4 subgroups) and the cardiogenetics departments in AMC (MCA included), UMCU and UMCG (Cg-group). Multiple logistic regression analysis was used to compare differences in agenda-topics between the Cg-group and all 4 non-Cg groups, and within the Cg group among clients with different backgrounds. 134 Cg and 332 non-Cg counsellees participated. Sociodemographic characteristics of the Cg-group were partly comparable to neurogenetic and oncogenetic groups. The majority of Cg-counsellees knew less than a year about the familiar disease (57% vs 29%) and most were referred by the medical specialist (55% vs. 24%) instead of taking initiative themselves. 27% Of the Cg-group were unable to formulate any agenda-topics, compared to 16% of the non-Cg group. On average 2.6 agenda-topics/counsellee were reported (no differences between groups). Cg-counsellees required less information on heredity/genetics (46% vs. 74%), more on clinical characteristics and daily living (47% vs. 19%) and they had the same informational needs regarding diagnostics and treatment (39%). Cg-counsellees with a positive attitude towards additional testing more often expressed the need for agenda-topics to be discussed. We conclude that the Cg-counsellees clearly differ from existing groups of counsellees in terms of personal characteristics, propensity to list agenda-topics and in terms of
specific informational needs, overall suggesting uncertainty due to lack of information. Clinical guidelines are urgently needed, that address the individual trade-off between quick decision-making on preventive options and adequate information exchange (dependent on specific needs) which inevitably requires more time than what is preferable from the first point of view.

**Chapter 7** is a case study describing an extended family from the AMC-cardiogenetic outpatient clinic that was suddenly confronted with the diagnosis of the LQTS in one of the relatives, following a severe arrhythmic event leading to brain damage in this relative. This exploratory study serves to illustrate the psychological impact on this family in the process of genetic counselling and testing for the LQTS.

All members of the third generation and their partners (n=11) were interviewed, the mutation carriers and their partners twice. In addition they completed measures for anxiety and depression three times in eighteen months. During the interviews these family members emphasised the damaged solidarity when the family is divided in carriers and non-carriers of a mutation in a LQTS predisposing gene. This demonstrates one way a family can react to the reality of being at risk for a potentially severe disease. Rewriting the family history and mourning for earlier deaths, also occurring in this family, seem other ways to deal with this. The distress scores, especially of the women, were moderate to clinically high, not because of their own chance to get a severe arrhythmia, but more due to their children's risk. These mothers and their spouses need educational even more than emotional support, to help them implement the radical changes of lifestyle of their carrier children, prescribed by the medical team.

Longitudinal psychological research in clients attending for predictive cardiological (ECG) and DNA-testing for the LQTS is presented in **chapter 8**. In a prospective study the extent and course of anxiety and depression caused by this new form of predictive genetic testing are described in applicants and their partners from the first consultation until 18 months after disclosure of the DNA-results.

Seventy-seven applicants and 57 partners completed measures of distress at three measurements. Especially those who received an uncertain ECG result are vulnerable for high levels of distress, at least in the short term. After DNA disclosure, the distress levels in the group of carriers remained high. The general distress levels in the whole group of applicants were largely restored within 18 months. However, the specific (disease related) distress scores in carriers remained increased at long term. Compared with non-carriers' partners, carrier partners had higher levels of disease related anxiety at all three assessments.

We conclude that cardiologic and molecular predictive testing for the LQTS leads to distress, especially at short term in carriers with an uncertain ECG at first visit and in their spouses. Therefore definitive DNA-results need to be given as soon as possible and ECG-testing may even be postponed until after DNA-disclosure in clients at low prior risk, based on age, medical and family history. At long term specific distress remains increased in carriers, probably also caused by the consequences of the disease itself (prophylactic treatment, rules of living and the carrier risk in offspring).
Part III Molecular diagnostic strategies

In chapter 9 research on the use of genotype-phenotype correlations to enhance efficiency in molecular genetic testing in the LQTS is described. The three most prevalent types of the LQTS, in the Netherlands as well as elsewhere, are caused by mutations in the KCNQ1, KCNH2 and SCN5A genes respectively. Most patients have private, heterozygous, mutations in one of these genes. Determination of the mutation in the index patient is a prerequisite for cascade screening in relatives.

Distinct genotype-phenotype correlations have been published. Age of onset, symptom related triggers, the ST-T segment morphology of the ECG, and the response to specific drugs are all linked to the aberrant gene involved.

In this study, we prospectively investigated whether the success rate of mutation detection in the genes first elected for analysis in LQTS index patients can be raised if known genotype-phenotype correlations are used.

Forty unrelated LQTS patients were included in this study. Clinical data on the characteristics mentioned above were collected from the patients and, if possible, from close relatives. ECG analysis was performed by calculation of QT intervals corrected for heart rate (QTc) and interpretation of the morphology of the ST-T segments. DNA analysis was performed in the diagnostic lab, by SSCP or DHPLC techniques and sequencing of aberrant conformers or elution profiles as described elsewhere. An experienced cardiologist, familiar with the LQTS decided the order of the three candidate genes to be screened based on clinical data and knowledge on prevalence and genotype-phenotype correlations. The added value of phenotypic data was evaluated independently by a second cardiologist, not personally involved in the management of these patients. As reference we used published data on prevalences of gene mutations in 262 European and American LQTS patients. Three screening strategies were compared in terms of costs and time needed to detect the causative mutation.

The genotype could be determined in 31 patients (78%, 10 KCNQ1, 18 KCNH2, 3 SCN5A). In 28 patients (70%, being 90% of genotyped cases) the mutation was depicted in the initially assigned gene. Using ECG-data exclusively, 74% of genotyped cases were predicted correctly, which is also significantly better than when prevalence data would have been used. Adding other phenotypic information resulted in correct prediction of the gene involved in 90% of genotyped cases. Inter-observer agreement was large.

Simultaneously screening all eligible genes is of course the best strategy to detect a maximum of mutations in short time, but is very costly and laborious. Screening only 1 candidate gene, based on phenotypical information, leads to a mere reduction of detection rates of 8%. Labour and costs are reduced by 80% however. We therefore recommend sequential screening of the important LQTS-genes with involvement of a knowledgeable cardiologists for phenotyping, to facilitate optimal use of resources.
Conclusion and future plans

The research described in this thesis focussed on the practical aspects of multidisciplinary care in cardiogenetic diseases associated with sudden cardiac death. Some gaps in knowledge have been filled and a lot of organizational problems have been solved, but many still exist and emerge, while we continue working with these patients and families.

A small but growing group of in this field knowledgeable cardiologists, clinical geneticists, genetic counsellors, psychosocial workers and molecular geneticists are joined in the ICIN (Interuniversitary Cardiologic Institute of the Netherlands) working group on cardiogenetics. Every six months this group meets to discuss questions regarding research and care in cardiogenetics, in general and in individual patients and families. All Dutch cardiogenetic outpatient clinics are represented in this working group. Guidelines for the organisation and further implementation of genetic testing and counselling (starting with a guideline on molecular testing and cascade screening in HCM in 2005) are being composed based on the results of scientific research and on consensus in this group, after consultation with the respective Dutch societies of Clinical Genetics and Cardiology (VKGN, NVVC) and of other stakeholders, including the families involved.

The results of psychological studies in LQTS-families show that predictive testing leads to enduring distress in certain subgroups. Research, preferentially randomised studies, is needed to investigate in which way and to whom psychological interventions should be offered. The ethical and psychological aspects of predictive testing in children are currently under investigation in the scope of a NWO-MCG study. The outcomes will be of importance for the foundation of clinical guidelines for predictive testing in this special group. Process and evaluation studies in (predictive) cardiogenetic counselling are also urgently needed, to enable the development of evidence-based guidelines for this time-consuming but important activity. This research should be initiated by clinical geneticists themselves, to build further foundations for their core-activities and to enable proper transference of these where indicated. Currently international research is starting to pay attention to organisational aspects of screening in hereditary arrhythmias and cardiomyopathies. The results of this research can also be used to (further) develop national guidelines and educational programs for the professionals involved.

In the meantime the ICIN has funded the development of a national web-based database for families and individual patients with hereditary arrhythmias and cardiomyopathies, supported by the professionals from the ICIN-working group on cardiogenetics. This database, in which privacy of individual patients and families is guaranteed, will serve as an important source for future (and current) research and patientcare. Two lines of research, on DCM (DIDCARE-study) and on HCM (ESCAPE-HCM-study) already profit from this database. In combination with DNA-banking (in development), the scope of research can be widened.

Education of cardiologists and clinical geneticist has been (and will be) organised in the scope of the CVOI/VKGN-educational program. Until now three successful courses, attended by members from both professional groups, have been given. Information on cardiogenetic diseases and (predictive) diagnosis is also provided on our recently launched website (www.
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cardiogenetica.nl). Education of cardiologists in training aimed at skills in genetic counselling and testing will have to be organised in the near future.

Some cardiologists, particularly the young ones that recently left the academic centres and who are familiar with the possibilities of molecular testing, are increasingly sending in DNA of their index patients for molecular testing themselves (although this is still officially prohibited). On this small scale it is still possible for us to get in contact with every one of them to check on the informed consent procedure, to explain the clinical implications and limitations of the results (if necessary) and to arrange the genetic counselling of the tested patient and the cascade screening in relatives at a later stage.

It should be questioned if direct requests for DNA-testing in index patients from cardiologists should be encouraged or discouraged. In oncogenetics requesting by oncologists, gynaecologists or surgeons is discouraged by the working group of clinical geneticist involved in this subject (WKO). The often unclear results of testing (uninformative results, unclassified variants), the need to keep knowledge concentrated in the academic clinical genetic centres and the perceived inabilities of other professionals regarding pre- and post-test counselling are being used as arguments (personal communications from WKO-members, May 2005). The same motivations could be used in the case of cardiogenetic testing, but the described willingness of most cardiologists to collaborate in stead of taking over, should lead to optimism in these regards and perhaps to a more liberal policy.

Particularly regarding requesting and guiding predictive testing a choice has to be made. When these tasks should continue to be performed by the clinical geneticist (and genetic counsellor) in collaboration with the cardiologist, doing justice to the results of our survey (chapter 3), an considerable enlargement of capacity will soon be needed. This will not be easy to realise in the near future. An alternative would be to establish an cascade screening program and organisation like the StOEH (Stichting Opsporing Erfelijke Hypercholesterolemie) for familial hypercholesterolemia, where genetic field workers (also to be educated) perform most of the job. No steps have been taken in this direction yet.

Regarding HCM in particular, reasons to propagate active tracing of all carriers as well as arguments to be reserved about it, can be brought forward. To the credit of active genetic screening are the general increased risk of dying suddenly and prematurely in asymptomatic carriers, currently without options for selection beforehand, and the possibilities of prevention. Arguments against active genetic screening in HCM are the general low annual risk of (premature) death of 1% in symptomatic patients and the fact that many HCM-patients have a normal life-span. Therefore it may be more sensible if we first try to asses modes of selection of high risk patients or families between the many relatively low risk patients and, if possible, to offer cascade screening only to the high risk families. The feasibility of this strategy is currently being evaluated in the scope of a national Zon/Mw ESCAPE-HCM-study.

The exact (age-dependent) increases of risks for heart failure and premature death in female DMD- and BMD-carriers should ideally also be determined by (international) epidemiologic research, to enable evaluation of the value of proactive tracing and cardiologic screening. The same applies to (still) asymptomatic carriers for myotonic dystrophy. If evaluation results in positive advises for tracing and screening, the scope of our outpatient cardiogenetic
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Clinic should be widened to include these patient-categories. Increased involvement of (neuromuscular orientated) neurologists will then be even more appropriate.

The research in this thesis was not aimed at the evaluation of the way in which identified carriers (and their parents, in the case of affected children) cope with the prescribed measures to prevent premature sudden death. This kind of research, investigating compliance and related subjects, will have to be initiated in the near future to eventually enable complete evaluation of the feasibility of active cascade screening for the various cardiogenetic diseases.

Research in cardiogenetics increasingly leads to clarification of fundamental mechanisms underlying primary arrhythmic diseases and cardiomyopathies. These results are of course also important for daily practice. Firstly, relatives of patients with a genetically clarified disease can be divided into risk carriers and those who are not at risk for sudden death. Consequently preventive measures can be exactly aimed at the right people and at more carriers than before. To patients with cardiac complaints that were formerly not understood, or to their surviving relatives, an explanation can often be given. Besides, we expect that improved therapeutic measures and cures for these diseases will be invented, based on increased genetic knowledge.

Regarding current pro's and con's of tracing relatives at risk for sudden cardiac death with genetic (or cardiologic) techniques, we think that active cascade screening can currently be justified, particularly when the enormous impact of sudden death in the young and its preventive options are taken into account. Future results of scientific studies could of course put the above into another perspective.

Every newly identified case, and every relative proved to be or not to be at risk, contributes (indirectly) to improved diagnostic and therapeutic options in next relatives and other patients with the diseases concerned. We therefore view the design and supply of the necessary care for these families as our professional duty. An essential part of this care is the uniform and unselfish registration of all diagnostic and genetic findings (and in the future of the effectiveness of preventive measures), without invasion of privacy. In this way, diagnostics and treatment can be improved all over the country. Luckily the first steps in this direction have already been taken.

In the past ten exciting years we could, enabled by the specific interest for these diseases in the AMC, contribute to the research into cardiogenetic disorders and also to the changing processes of care, often overtaken by the fast developments. Standard procedures had to be readjusted before evaluation had been possible and under constant pressure of capacity problems. This was, and still is, caused by the 'birth and growing up' of cardiogenetic diseases on the one hand and by the strictly formulated social requirements of this kind of care (particularly regarding the informed choice/consent procedures).

These contributions are in our view not only relevant for this discipline, but learning from the careful approach in cardiogenetics, like that in oncogenetics, could be helpful in the development of genetic care in other fields of medicine, where genetic inventions increasingly induce new options for tracing, prevention and therapy.