Mortality in inherited cardiac diseases: directing care in affected families
Nannenberg, Eline

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Chapter 1

General introduction and outline of the thesis
**GENERAL INTRODUCTION**

Cardiovascular diseases are a major cause of morbidity and mortality worldwide. Despite a major decline of the incidence of ischemic heart disease in the past decades, heart disease remains the leading cause of death in the USA. Cardiovascular diseases in the Netherlands account for 27% of all deaths and are therefore one of the main causes of death. Part of cardiovascular mortality and morbidity is the result of an inherited cardiac disease. Death from inherited cardiac diseases can be due to heart failure or it can be sudden. Exact numbers of the total burden are unknown, but estimates can be made based on studies of victims of sudden cardiac death (SCD), and on prevalence and mortality risks of the different inherited cardiac diseases.

According to worldwide estimates, the incidence of SCD -defined as unexpected death from cardiac causes within 1 hour of the onset of symptoms- ranges between 180,000 and >450,000 cases annually in the United States. In the general Dutch population, the yearly incidence of sudden death (age range: 20-75 years) was estimated 1 in 1000 inhabitants, accounting for 18.5% of all deaths. Under the age of 40 years, the incidences of sudden death are estimated at 1.3-8.5 per 100,000 person-years. In Western countries, the overall incidence of SCD is estimated at 0.9-2.8 per 100,000 person-years. In the Netherlands, we are confronted with approximately 250 young SCD victims each year. It is known that inherited cardiac diseases play an important role in the cause of SCD in the young and are accountable for approximately 40-60% of SCD cases under the age of 50 years. The large variation of the percentage of SCD attributable to an inherited cardiac disease in literature depends on the age of inclusion of the victims, the population that was studied (population based or tertiary referral center), the patients that were included (the SCD victims or first degree family members), and the type of data collection (for instance autopsy reports or molecular autopsy results).

Roughly, inherited cardiac diseases can be subdivided in inherited arrhythmia syndromes and inherited cardiomyopathies. Estimated prevalences in the general population of the different inherited cardiac diseases vary between 1:250 to 1:10000 (Table 1). This suggests a total prevalence of 57,653 to 162,433 patients with an inherited cardiac disease in the Netherlands.

According to the European Society of Cardiology, cardiomyopathies are categorized into different subtypes: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathies (RCM), arrhythmogenic (right ventricular) cardiomyopathy (A(RV)C), and unclassified cardiomyopathies. Each subtype can then be subdivided in genetic and non-genetic forms. The most common inherited arrhythmia syndromes are the long QT syndrome (LQTS),
Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Idiopathic Ventricular Fibrillation (IVF), in the Netherlands in particular caused by a specific risk haplotype on chromosome 7q36 harboring the DPP6 gene.32 Most inherited cardiac diseases have an autosomal dominant pattern of inheritance and are characterized by incomplete penetrance and variable expression: patients can be asymptomatic throughout life to severely affected from young age onwards. Inherited cardiac diseases are associated with a substantial mortality risk, due to arrhythmias (SCD), heart failure, and embolic stroke.33 In the cardiomyopathies, the relative contribution of SCD to overall mortality differs between the different forms of cardiomyopathy. In ARVC, the relative contribution of SCD to overall mortality is highest, followed by HCM, and then DCM, in which heart failure is the main cause of death.34 In the inherited arrhythmia syndromes, the first presentation of the disease in a patient

Table 1. Prevalences, estimated Dutch patients and mortality risk of inherited cardiac diseases.

<table>
<thead>
<tr>
<th>Inherited Cardiac Disease</th>
<th>International Prevalence</th>
<th>Estimated Dutch patients (based on population of 16,900,000 inhabitants)</th>
<th>Mortality Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>1:250-1:500(^{16,17})</td>
<td>67600-33800</td>
<td>0.3-3% yearly (treated)(^{18,19})</td>
</tr>
<tr>
<td>DCM</td>
<td>1:250-1:2500(^{20}) *</td>
<td>67600-6760</td>
<td>Depending on presentation and etiology</td>
</tr>
<tr>
<td>ARVC</td>
<td>1:1000-1:5000(^{31})</td>
<td>16900-3380</td>
<td>~2% yearly(^{22,23})</td>
</tr>
<tr>
<td>LQTS</td>
<td>1:2000(^{24})</td>
<td>8450</td>
<td>6-8% by age 40(^{25}) (untreated)</td>
</tr>
<tr>
<td>BrS</td>
<td>1:2000-1:5000(^{36})</td>
<td>8450-3380</td>
<td>0-5% yearly(^{27})</td>
</tr>
<tr>
<td>CPVT</td>
<td>1:10000(^{38})</td>
<td>1690</td>
<td>30% -50% (untreated) by age 40(^{29,30})</td>
</tr>
<tr>
<td>IVF (risk haplotype on chromosome 7)</td>
<td>?</td>
<td>193 living carriers in the Netherlands at present</td>
<td>At age 50, 30% SCD (untreated)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>57653-162433</td>
<td></td>
</tr>
</tbody>
</table>

*including non-hereditary forms of DCM

Abbreviations: HCM=Hypertrophic cardiomyopathy, DCM=Dilated cardiomyopathy, ARVC=Arrhythmogenic right ventricular cardiomyopathy, LQTS=Long QT syndrome, BrS=Brugada syndrome, CPVT=Catecholaminergic polymorphic ventricular tachycardia, IVF=Idiopathic ventricular fibrillation, SCD=Sudden cardiac death, ACA=Aborted cardiac arrest
can be aborted cardiac arrest or SCD at a young age.\textsuperscript{35} Since this is a devastating event for the patient and his/her family, it is of outmost importance to identify the subjects at risk for (sudden) cardiac death. Especially, since treatment or preventive options are available for most of the inherited cardiac diseases to reduce mortality risk and subsequently save many patient years. For LQTS and CPVT patients for instance, beta blockers have been proven very effective. For Brugada syndrome, avoiding certain medications and lowering fever can prevent malignant arrhythmias. In inherited arrhythmia syndromes, with a high risk of fatal arrhythmias, medicine and/or an implantable cardioverter defibrillator (ICD) have proven to be the designated therapy to prevent death from these arrhythmias.\textsuperscript{36} For the cardiomyopathies, treatment is based on the individual phenotype of patients and ranges from pharmacological therapy, surgical management to implanting an ICD (in case of a high risk of arrhythmias).\textsuperscript{37,38} ICDs have been proven effective in preventing SCD from arrhythmias in cardiomyopathies, but for other forms of preventive treatment the effect on morbidity and mortality is still not elucidated. However, promising studies are currently performed to effectuate this in the future.\textsuperscript{39-42} The last decades, important advances have been made in unravelling the genetic basis of inherited cardiac diseases. This enables us to perform genetic cascade screening and to identify mutation carriers at risk for developing the disease and for (sudden) cardiac death.\textsuperscript{43} Subsequently, mutation carriers are advised to stay under cardiac surveillance to assess risk factors for (sudden) cardiac death, take preventive measures or start treatment. For these -often asymptomatic- carriers and their doctors it is important to have knowledge about the mortality risk, but this risk is ill defined. With more accurate knowledge about the (individual) mortality risk of the disease, patients can be educated about their prognosis, the timing of (preventive) treatment and screening can be determined, and reproductive choices can be made.

In the next paragraphs, we will address the mortality risk, and factors influencing this risk in inherited cardiac diseases (described in this thesis). Furthermore, we will describe a method to assess the mortality (family tree mortality ratio (FTMR)).

**Mortality risk and factors influencing the mortality risk of inherited cardiac diseases**

**HCM**

In early studies, the overall annual mortality rate for HCM was estimated up to 6%.\textsuperscript{19} This high percentage was mainly due to the inclusion of severely affected patients referred
to selected tertiary centers. Over the past decade, more balanced and lower annual mortality rates have been reported in treated HCM patients, with an estimated annual all-cause mortality of less than 3% and an annual sudden death mortality of 1% or less in cohorts with less selection on outcome.18,19,44 Events are most frequent in adolescents and young adults, but may occur at all ages. Within the HCM population, subgroups with a higher incidence of SCD can be identified based on clinical risk stratification.45,46 The main clinical risk factors that are associated with an increased mortality risk are a prior cardiac arrest, a family history of SCD, abnormal blood pressure response during exercise, unexplained syncope, non-sustained ventricular tachycardia (NSVT) on 24 hour Holter monitoring, and a maximal wall thickness of ≥30 mm. Other described putative risk factors are coronary artery disease, ‘burnt out’ disease, resting LV outflow tract obstruction, and diffuse late gadolinium enhancement on MRI. No clear association between gender and SCD have been observed.45 Recently, a novel clinical risk prediction model was described (HCM Risk-SCD) to provide accurate individualized estimates for SCD risk using seven clinical parameters; age, maximal left ventricular wall thickness, left atrial diameter, left ventricular outflow tract gradient, family history of SCD, non-sustained ventricular tachycardia, and unexplained syncope.47 Genetics has not been proven effective in discriminating patients at risk for death, except for double or compound heterozygous sarcomeric mutations (in up to 5% of HCM patients). The presence of two affected alleles is associated with a more severe phenotype, including a higher risk of SCD.48,49

DCM

DCM is a heterogeneous disease with various underlying causes. The inherited form usually presents in patients between 30-60 years of age.20 The mortality risk in DCM depends on the presentation and etiology of the disease. Early studies on survival reported higher mortality risks than more recent studies in symptomatic patients reporting an average five-year mortality of 20%.50 Heart failure is the most frequent cause of death, but thromboembolism and SCD also contribute to this mortality. The annual mortality rates depend on the severity of heart failure (NYHA functional class): from 12-15% in class I-II, to 60% in class IV. In class I-II, 50-60% of deaths is sudden, compared with 20-30% of the deaths in class IV patients, where most patients die of heart failure.34 Described risk factors that are associated with an increased mortality are left ventricular dysfunction, NSVT, midwall late gadolinium enhancement, a previous cardiac arrest, and unexplained syncope. Mutations in the LMNA- and PLN-gene -causing DCM - are associated with an increased mortality risk (both sudden and heart failure related death) compared to other genetic forms of DCM.51,52
**LQTS**

In LQTS, the three most prevalent (sub-) types are long QT syndrome type 1 (LQTS1), type 2 (LQTS2), and type 3 (LQTS3). Each type has its own phenotypic characteristics. In patients with LQTS1 can develop symptoms, mostly triggered by physical activity (among which swimming), in LQTS2 symptoms are mostly triggered by emotional stress and auditory stimuli, and in LQTS3 symptoms mostly occur during rest. While LQTS1 patients exhibit a high rate of cardiac events of any type during childhood and adolescence, the cumulative mortality is similar in all three types at 6-8% before the age of 40 years in patients and their relatives. In patients from the LQTS registry, between 0 to 18 years, LQTS1, LQTS2, and LQTS3 patients had a cumulative mortality rate of 2%, 3%, and 7% respectively. From 19 to 40 years, LQTS1, LQTS2, and LQTS3 patients had a mortality rate of 5%, 7%, and 5% respectively. Male gender is associated with an increased risk of cardiac events (syncope, aborted cardiac arrest or SCD) before the age of 16, whereas after this age females have an increased risk of events. During lifetime, males with LQTS have a reported mortality rate of 13%, females of 21%. Females with LQTS2 have a higher risk of events in the first year post-partum. Other important clinical risk factors are the length of the QT-interval, prior syncope, and prior aborted cardiac arrest. Environmental factors that can increase the risk of SCD, through prolongation of the QT-interval, are among others QT-prolonging drugs. Several studies have shown that there are gene-specific factors affecting the risk of SCD in patients with LQTS; the location and biophysical function of the mutation in the ion channel is an important determinant of cardiac events. LQTS1 patients with transmembrane versus C-terminus mutations and patients with mutations having a dominant-negative versus haploinsufficient impact on ion channel function are at increased risk for cardiac events. In LQTS2 patients, mutations in the transmembrane pore region are associated with a higher risk of cardiac events compared with non-pore mutations. The additional presence of single nucleotide polymorphisms (SNPs) in NOS1AP have been associated with an increased severity of disease, whereas a specific SNP in the KCNH2 gene and a SNP in KCNQ1 results in a protective effect in LQTS patients. SNPs in the 3’ untranslated region of the KCNQ1 gene have been shown to modify allelic expression and therefore disease expression. Also common variants in the SCN5A (S1103Y in black individuals) and KCNE1 gene (D85N in white individuals) are associated with an increased risk of arrhythmias, in combination with QT-prolonging drugs. Furthermore, patients with digenic or compound mutations are at more severely increased risk of cardiac events.
**Brugada syndrome**

In Brugada syndrome, events occur predominantly between the third and fourth decade, typically at rest or during sleep. Brugada syndrome is more common in men (approximately 80%). The annual event rate in asymptomatic individuals with a spontaneous abnormal baseline ECG ranges between 0 and 5%, with the highest event rates reported in earlier studies, probably biased for more severe phenotypes. The annual event rate in asymptomatic patients with a drug induced Brugada pattern is almost 0% in all studies. Risk stratification in Brugada syndrome is ill defined. The most well defined risk factors for SCD nowadays are syncope of unknown origin, and a history of (non-sustained) VT/ VF, and to a lesser extend a spontaneous coved type ST-segment elevation. Male gender is in some studies associated with an increased risk of arrhythmic events. Fever and certain medications are important environmental risk factors. Genetic factors have also been described, with nonsense mutations in the \( \text{SCN5A} \) gene giving rise to an increased frequency of syncope and conduction abnormalities compared to missense mutations. SNPs in the \( \text{SCN5A} \) promoter region were described to be associated with variable conduction velocity in the southeast Asian population. Patients with compound mutations in the \( \text{SCN5A} \) gene can present at a young age, with a severe phenotype (usually characterized by severe conduction slowing).

**CPVT**

CPVT is a highly lethal disease if left untreated, with 80% of CPVT patients developing symptoms (syncope, VT or VF) by age 40 and mortality rates up to 30-50%. Also in patients using beta-blockers, the 8-year cardiac event rate was estimated 27%. The median age of lethal events ranges between 13-28 years. At present, risk stratification for CPVT is poorly defined. A previous aborted cardiac arrest, a younger age at diagnosis, and absence of betablockers are independent predictors for cardiac events. Also, an abnormal exercise stress test with couplets or more successive premature ventricular contractions was associated with an increased risk of a future cardiac event. Male carriers have a 4-fold increased risk of cardiac events compared to females. One series showed that mutation carriers with a C-terminal mutation have an increased risk of NSVTs compared to patients with a N-terminal mutation.

**IVF caused by a risk haplotype on chromosome 7**

Carriers of the risk haplotype for idiopathic VF (harbouring the DPP6 gene) have a high risk of ventricular arrhythmias. At age 50 years about 30% of patients have experienced (aborted) SCD, often occurring without prior symptoms. The arrhyth-
mias almost exclusively occur between 20 and 50 years, and the risk is higher in males compared to females (unpublished data). Currently, risk stratification is not possible. As a result, we recommend implantation of an ICD to all carriers of the risk haplotype between 20 and 50 years.

**Founder mutations**

A founder mutation is a gene mutation that emerged many generations ago in an ancestor in a (geographic isolated) population and has spread subsequently to the next generations. Nowadays, this can be reflected in an increased frequency of the founder mutation in a specific geographical region (Figure 1). Several founder mutations have been identified in a number of inherited cardiac diseases worldwide in the past decades. In the Netherlands, founder mutations have been described in HCM, DCM, ARVC, arrhythmogenic cardiomyopathy (ACM), Brugada syndrome/SCN5A overlap syndrome, CPVT, and

![Postal code map showing the unevenly regional distribution of the PLN c.40_42del mutation carriers in the Netherlands. The number of mutation carriers per region is shown (in parenthesis: the number of postal code regions, 90 in total). On average, each region contains 180,000 inhabitants.](image-url)
idiopathic VF (Table 2). For some diseases, for instance LQTS, recurrent mutations have been described, but when haplotyping has not been performed, classifying them as definite founder mutation is difficult because there is always the possibility of a hotspot where mutations occur preferentially. For some inherited cardiac diseases, one founder mutation comprises a large part of all causal mutations for that specific disease. For instance, the c.2373dup mutation in the MYBPC3 gene was identified in nearly 25% of all Dutch HCM cases in the first published study. Furthermore, the c.40_42del mutation in the PLN gene, is found in 10–15% of Dutch patients with dilated cardiomyopathy or arrhythmogenic cardiomyopathy. The estimated carrier frequency of this mutation in the general population in the north of the Netherlands is estimated to be 1 in 1400. Carriers of the above mentioned founder mutations are the ideal subjects to study genotype-phenotype correlations, the role of modifying factors underlying the clinical variability, and disease mortality, because they have a similar genetic background and the number of carriers is ample.

The ‘Family tree mortality ratio’ (FTMR) method
In general, one can study mortality with different methods, in prospective or retrospective (historical) patient cohorts. In autosomal dominant inherited diseases, it is possible, to assess the mortality in large families, going back many generations age, where mutation carriers are identified by Mendelian randomization, in times when the disease was not known, its genetic basis not suspected, and treatment was not available. This method is called the family tree mortality ratio (FMTR) method.

The FTMR method was first described in literature in 1991, and in the following years used to describe the mortality of protein C deficiency, factor V Leiden, Huntington disease, and hereditary skin cancer. In 2001, Sijbrands et al., used the method to study the mortality of familial hypercholesterolemia over two centuries. The starting point of the method is a known and identical autosomal dominant mutation in at least two index cases, who preferable share the same DNA haplotype, implying the presence of a common ancestor (Figure 2; step 1). Genealogical searches can then be started to find a common pair of (distant) ancestors. Taken Mendelian inheritance into account, all persons linking the two index patients, in other words the persons who transmitted the mutation to the next generation, can be defined as obligate (100%) carriers in the pedigree (Figure 2; step 2). Furthermore, all siblings and children of proven and obligate carriers have a 50% probability of carrying the mutation. In the top of the pedigree, one of two common ancestors was the carrier introducing the mutation to the offspring (Figure 2; step 3). This ancestor pair has also a 50% probability of
### Table 2. Established founder mutations in inherited cardiac diseases in the Netherlands.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Mutation</th>
<th>Region in the Netherlands with highest prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>MYBPC3</td>
<td>c.2373dup; p.(Trp792Valfs*17)</td>
<td>North-West</td>
</tr>
<tr>
<td></td>
<td>MYBPC3</td>
<td>c.2864_2865del; p.(Pro955Argfs*95)</td>
<td>South-West/Middle</td>
</tr>
<tr>
<td></td>
<td>MYBPC3</td>
<td>c.2827C&gt;T; p.(Arg943*)</td>
<td>South-West</td>
</tr>
<tr>
<td>HCM</td>
<td>TNNT3</td>
<td>c.4333C&gt;T; p.(Arg145Trp)</td>
<td>Randomly distributed</td>
</tr>
<tr>
<td>DCM</td>
<td>PLN</td>
<td>c.40_42del; p.(Arg14del)</td>
<td>North</td>
</tr>
<tr>
<td>Cardiomyopathy and myopathy</td>
<td>DES</td>
<td>c.38C&gt;T; p.(Ser13Phe)</td>
<td>North</td>
</tr>
<tr>
<td>(DCM/LVH/RCM/ARVC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy and myopathy</td>
<td>DES</td>
<td>c.1024A&gt;G; p.(Asn342Asp)</td>
<td>South-West</td>
</tr>
<tr>
<td>(ARVC/LVH/cardiomyopathy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARVC</td>
<td>PKP2</td>
<td>c.235C&gt;T; p.(Arg79*)</td>
<td>North</td>
</tr>
<tr>
<td></td>
<td>PKP2</td>
<td>c.397C&gt;T; p.(Gln133*)</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>PKP2</td>
<td>c.2386T&gt;C; p.(Cys796Arg)</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>PKP2</td>
<td>c.2489+1G&gt;A</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>PKP2</td>
<td>c.2489+4A&gt;C</td>
<td>Middle</td>
</tr>
<tr>
<td></td>
<td>PKP2</td>
<td>c.1211_1212insT; p.(Val406Serfs*4)</td>
<td>West</td>
</tr>
<tr>
<td></td>
<td>PLN</td>
<td>c.40_42del; p.(Arg14del)</td>
<td>North</td>
</tr>
<tr>
<td>LQTS3</td>
<td>SCN5A</td>
<td>c.5302A&gt;G; p.(Ile1768Val)</td>
<td>Unknown</td>
</tr>
<tr>
<td>LQTS3/Brugada syndrome</td>
<td>SCN5A</td>
<td>c.5385_5387dup:p.(Tyr1795_Glu1796insAsp)</td>
<td>North</td>
</tr>
<tr>
<td>(SCN5A overlap syndrome)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brugada syndrome/cardiac</td>
<td>SCN5A</td>
<td>c.2582_2583del; p.(Phe861Trpfs*90)</td>
<td>East</td>
</tr>
<tr>
<td>conduction syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCN5A</td>
<td>c.5228G&gt;A; p.(Gly1743Glu)</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>SCN5A</td>
<td>c.4850_4852del; p.(Phe1617del)</td>
<td>South-East</td>
</tr>
<tr>
<td>IdiopathicVF</td>
<td>DPP6</td>
<td>risk haplotype (suggestive for a founder</td>
<td>Middle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mutation) on chromosome 7q36</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>risk haplotype specific variant:</td>
<td></td>
</tr>
</tbody>
</table>

Nomenclature according to hgvs using the following reference sequences: NM_000256.3(MYBPC3); (NM_000363.4(TNNI3);(NM_002667.3(PLN);(NM_001927.3(DES);(NM_004572.3(PKP2); (NM_198056.2(SCN5A); NM_001290252.1(DPP6);c.-340C>T.
carrying the mutation. All second degree relatives of proven and obligate carriers have a 25% probability of carrying the mutation. This way, a few index cases (with a minimum of two) are the source of a much larger number of obligate and potential carriers going back many generations in the past. In addition to the analyses in large pedigrees -going back many generations ago- it is also possible to study the mortality of the disease in small (nuclear) families, including all first-degree relatives of the index patient (Figure 2; step 1).

Subsequently, of all included persons in the analyses (at least the 50% probability mutation carriers) the date of birth and the date of death are obtained. In the Netherlands, the official records of birth, marriages, and deaths after 1811 are excellently preserved in municipal and state archives (Figure 3). Before 1811, parish registers can be used.

The mortality in the pedigree (observed mortality) will then be compared with the mortality in the Dutch population (expected mortality), standardized for age, sex, and calendar period. The expected mortality is calculated by multiplying the total number of years lived by the study population with the age and gender specific mortality rates of the Dutch population for each calendar period, available at ‘Statistics Netherlands’. The ratio of the observed mortality in the pedigree and the expected mortality from the general population is the Standardized Mortality ratio (SMR). A SMR of 1 means that the mortality in the patient population and in the general population are equal. If the SMR is larger than 1 there is excess mortality in the patient population. If the SMR is less than 1 there is longevity in the patient population compared to the general population. (Thesis E.T.M. Hille: The ‘family tree mortality ratio’: a study of the natural history of hereditary disorders in past and present)

With this method, patients are not selected on their severe clinical outcome (but on their
place in the pedigree) and in times when the disorder was fully unidentified. Hence, by using this pedigree method we can include many relatives from times before treatment was available and have follow-up information on death without the risk of selection bias. Especially the inclusion of untreated patients, makes the FTMR a very elegant and attractive way to study the natural history of the disease and provide (age-specific) mortality rates unaffected by treatment.

Figure 3. Example of a death certificate in the 19th century.
Chapter 1
OUTLINE OF THE THESIS

Knowledge about the mortality of (cardiac) diseases is important to educate patients and their relatives, to establish and optimize the effectiveness of treatment and screening, and to inform patients about reproductive choices. This thesis includes studies that describe the mortality of different inherited cardiac diseases, the effect of ascertainment bias on the results of reported mortality in literature, and the results of 15 year prenatal diagnosis and preimplantation genetic diagnosis for inherited cardiac diseases in the Netherlands.

The introduction in chapter 1 gives an overview of what is known about the mortality of different inherited diseases and explains a method to assess mortality, i.e. the family tree mortality ratio (FTMR) method. In chapter 2, we present an overview of different HCM causing founder mutations in the Netherlands. In chapter 3 the mortality risk of HCM, caused by mutations in the \textit{MYBPC3} gene is determined with the FTMR method. Chapter 4 describes the mortality risk of 6 inherited arrhythmia syndromes, assessed with the FTMR method. In chapter 5, we focus on gender differences in major cardiac events and the mortality risk in lamin A/C (\textit{LMNA}) mutation carriers. Chapter 6 describes the effect of ascertainment bias (selection bias in including patients in studies) on mortality in inherited (cardiac) diseases. In chapter 7, a retrospective overview of 15 years prenatal diagnosis and preimplantation genetic diagnosis for inherited cardiac diseases in the Netherlands is presented. Finally, in chapter 8, the results of the previous chapters are discussed, put into perspective, and summarized.
REFERENCES


Chapter 1

Introduction


Chapter 1


Introduction


