Premature atherosclerosis: Sounds familial?
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Citation for published version (APA):

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Chapter 1

Introduction and outline

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INTRODUCTION

Cardiovascular disease
Currently, cardiovascular disease (CVD) is the leading cause of death and disability in western society. It causes nearly half of all deaths in Europe and is estimated to cost the EU economy €192 billion a year [1,2]. To date, a plethora of preventive measures, such as cholesterol lowering medication, platelet aggregation inhibitors and programs supporting smoking cessation, have attempted to reduce the burden of CVD. However, current strategies aimed at lowering systemic risk factors have only achieved a 20–30% reduction in the cardiovascular event rate [3].

The primary underlying mechanism of CVD is atherosclerosis. Atherosclerosis is a chronic disease, characterized by a combination of lipid accumulation, inflammation of the vessel wall and thrombotic reactions. Nevertheless, atherosclerosis is also a degenerative process and as a consequence of ageing, eventually it will occur in all of men. However, the rate and progression of the process will depend on the exhibition of certain risk factors.

Currently, individual cardiovascular risk is calculated by means of these risk factors, the most important being: age, sex, blood pressure, cholesterol, diabetes mellitus, obesity and smoking. Historically, these risk factors were obtained via large observational cohort studies, such as the Framingham Heart Study [4] and the Systemic Coronary Risk Evaluation (SCORE) [5]. Via mathematical algorithms these risk factors can be combined and, consequently, it is possible to express everyone’s individual risk for cardiovascular events in a percentage.

Unfortunately, it is not that simple. Certain groups will have an over- or underestimation of their actual risk. Specifically, cardiovascular risk will be underestimated by the current cardiovascular risk algorithms in those at younger age, those with only one risk factor and those with a familial predisposition to CVD.

Premature cardiovascular disease

Despite higher event rates and cardiovascular burden in individuals at a more advanced age; it represents a greater challenge in individuals who develop CVD at a very young age. In fact, of all patients with CVD, 6-10% is affected at a very young age [6]. This so-called premature CVD is even a greater problem, because at that stage of life, the medical, social and financial consequences are considerably greater. It is a challenge for the treating physician to properly guide these patients, since their life expectancy is probably expressed in decades and not in years. In 2009 in the Netherlands, there were approximately 80,000 hospitalizations due to CVD in patients younger than 55 years. Although the overall mortality due to CVD and coronary artery disease (CAD) is reduced over time, it is currently observed that this does not account for patients affected before the age of 55 years. As can be appreciated from figure 1, since 1980 in the Netherlands the relative reduction of CAD is smallest in the younger patients. Multiple observational studies in Western countries suggest that the reduction in mortality rates in this young group has stagnated and warn for a possible increase in the future [7-9].
The number of patients with a myocardial infarction is adjusted for the number of inhabitants in the Netherlands. The number in 1980 is set at 100, the other numbers are calculated relative to 1980. Numbers were adapted from the Dutch Heart Foundation and the Dutch Central Bureau of Statistics.

Premature CVD or CAD, usually defined as a cardiovascular event occurring before the age of 50 or 60 years, is associated with substantially greater heritability [10] than CVD or CAD at advanced age. Also, the presence of traditional risk factors —such as smoking, hypertension and dyslipidemia— is in these individuals generally low at time of their first event [11]. Therefore, it is suggested in literature that such premature CVD is more often associated with heritability of the disorder and tends to cluster within families [12,13]. For instance, the risk of developing a
cardiovascular event in a sibling of a patient with premature CVD is much higher than might be expected by the shared environmental risk factors within a family [14]. Also, since the manifestation of the disease is different across age, with less multi-vessel disease in the young [15], other mechanisms may underlie familial premature CVD.

Despite the effort that has been made in this research field, the cause of most cardiovascular events mostly remain unidentified. In some cases genetic disorders can be found, such as low density lipoprotein (LDL) cholesterol receptor deficiencies in familial hypercholesterolemia or mutations of the β-myosin heavy chain gene in families who suffer from hypertrophic cardiomyopathy.

Nevertheless, most of the time, a specific genetic disorder remains unknown, despite the obvious genetic predisposition in these families. Therefore, patients with premature CVD are mostly considered as the same patient group as patients with CVD at advanced age, which is merely a simplification of the complex disease.

One of the consequences of this concept is that premature CVD is treated in the same way as CVD in the elderly. The rationale of treatment after a cardiovascular event is to prevent recurrent events. Nevertheless, if the underlying mechanism differs in these young patients, preventive strategies might not be able to prevent recurrent events.

A family history of premature cardiovascular disease

A premature cardiovascular event does not only have its effect on the affected probands, but also on their relatives. Indeed, a family history of premature CVD or CAD is an independent risk factor for CVD [16,17]. The associated risk increases further when relatives are affected at a younger age [18,19]. After a cardiac death or a premature cardiovascular event within a family, the unaffected relatives of the patient suddenly become aware of their risk. Unfortunately, this awareness decreases quickly and most relatives are not tested for cardiovascular risk factors or genetic defects [20]. Those who consult a general practitioner or a cardiologist for a cardiovascular risk assessment face another problem.

The traditional risk score algorithms, such as the Framingham Risk Score, which are most used for cardiovascular risk prediction, poorly predict this risk; not only in general, but even more in relatives of patients with premature CVD [21]. The latter is mainly attributable to the fact that age is the most potent factor determining CVD, thereby falsely minimizing the risk particularly in younger siblings of high risk families. In addition, risk score algorithms use markers of risk instead of identifying disease itself. Furthermore, if we assume an important hereditary component in these families, not all relatives will be exposed to the same risk. Unfortunately, in absence of a known genetic disorder, a family history of premature CVD or CAD reveals families at risk without identifying individuals at increased risk. For instance, even in case of a monogenic inheritance pattern, each first degree relative has only a 50% chance of inheriting the same genetic defect. Therefore, if the true propensity for CVD or CAD is unknown in that individual, a decision regarding treatment might as well be made by flipping a coin. This emphasizes the need to further refine the risk assessment among siblings in these families.
Consequently, investigators keep on searching for new biomarkers and tools for assessing subclinical disease, to identify subjects with early onset CVD. The detection of latent atherosclerotic disease can assist in the identification of individuals at increased risk and thereby assist in individual decisions regarding preventive treatment [22]. Imaging of the vasculature provides a method to evaluate the vascular vulnerability towards atherogenesis, encompassing both hereditary and environmental factors. Indeed, previous studies have also shown that individuals with a family history of premature CVD exhibit increased subclinical atherosclerosis. In 1,662 individuals, a family history of premature CAD was shown to be independently correlated with carotid intima-media thickness, whereas family history of late-onset CAD was not [23]. Others studies confirm these findings with regard to intima-media thickness, not only in adults [24] but even in children with a family history [25]. Secondly, coronary artery calcification (CAC) is also increased in those with a family history of premature CVD [26]. The MESA (Multi-Ethnic Study of Atherosclerosis) revealed that with a younger age of the affected proband, the stronger the association was with CAC in relatives. The same holds true for the number of affected relatives [27]. As such, cardiovascular imaging might assist risk stratification within families with premature CVD.
Chapter 1

OUTLINE

Part I
A family history of premature CVD or CAD is an independent risk factor for future cardiovascular events in individuals without any CVD, but it is unclear whether a family history of premature CVD also increases the risk for recurrent events in patients who already had a cardiovascular event. Part I of this thesis addresses this issue together with overview of the cardiovascular risk for relatives conveyed by using different age criteria for a family history of ‘premature’ CAD. Chapter 2 provides a systematic review of prospective cohort studies, which evaluate cardiovascular risk by using different age criteria for a family history of premature CAD. Furthermore, we identified definitions of a family history of premature CAD used in various risk score algorithms and guideline documents and validated these.

In chapter 3, we explored in a cohort of patients with premature CVD whether a family history of premature CVD is associated with an increased risk for recurrent cardiovascular events. Since these results were obtained from a rather small cohort, we tried to confirm our findings in a cohort of 3,102 patients with premature CAD. These results are presented in chapter 4. Then, we have extended these findings in chapter 5, in which we show that an increased risk for recurrent events specifically accounts for arterial thrombotic events.

Part II
Despite the fact that a family history of premature CVD or CAD is an established risk factor for cardiovascular events, traditional risk score algorithms poorly predict cardiovascular risk in these individuals. Therefore, novel tools for risk assessment are continuously developed to assist in this matter. In part II of this thesis we describe measurements of subclinical atherosclerosis and vascular function in individuals with a family history of premature CAD. In chapter 6, we review current literature concerning subclinical atherosclerosis in individuals with a family history of premature CAD. Not only macrovascular atherosclerotic disease, but also microvascular abnormalities are present in individuals with a family history of premature CAD. This is shown in chapter 7, in which we evaluate microvascular function - assessed via sublingual sidestream dark field imaging in a case control study with patients with premature CAD, their unaffected first degree relatives and healthy controls. To assess macrovascular function in these three groups, we have measured arterial stiffness via pulse wave velocity in chapter 8. Next to vascular function, assessment of subclinical atherosclerosis is a possibility to estimate cardiovascular risk. Presence of CAC which is known to improve risk prediction on top of traditional risk score algorithms is increased in individuals with a family history of premature CAD. However, assuming a hereditary disorder, not all relatives will have an increased risk. Therefore, we assessed in chapter 9 the utility of CAC scoring in risk stratification among families with premature CAD. Because it is unclear whether preventive treatment of individuals with elevated CAC is beneficial in terms of cardiovascular outcome, we evaluated in chapter 10 whether individuals with a family history of premature CAD and elevated CAC benefit from preventive statin treatment. Chapter 11 summarizes the thesis and gives future perspectives.
REFERENCES


