Premature atherosclerosis: Sounds familial?
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Chapter 11

Summary and future perspectives

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SUMMARY

This thesis focuses on families with premature cardiovascular disease (CVD) and more particular, in most chapters, families with premature coronary artery disease (CAD). Throughout this thesis, three main questions are explored:

- Do patients with premature CVD or CAD and a family history of premature CVD have an increased risk for recurrent events?
- Do individuals with a family history of premature CAD have increased atherosclerotic burden and microvascular dysfunction compared to those without a family history?
- Is it possible to use coronary artery calcium (CAC) scoring in families with premature CAD for individual risk stratification?

Part I: The effect of a family history on cardiovascular events

Chapter 1 gives an introduction to this thesis. At first, we describe the epidemiology and the major risk factors contributing to atherosclerotic CVD. This is followed by a short discussion about the differences between CVD at advanced age versus the CVD in the young (premature CVD). Finally, the relevance of a family history of premature CVD and CAD in cardiovascular risk prediction is discussed.

In chapter 2 we provide a systematic review of prospective cohort studies, which evaluate cardiovascular risk conveyed by using different age criteria for a family history of ‘premature’ CAD. We searched PUBMED and EMBASE database and identified 15 prospective cohort studies. We found that there is an inverse relation between the associated risk increase for relatives and the age of onset of a CAD event in probands (hazard ratio 4.5 (95% confidence intervals (CI) 1.3 - 15.4) for probands affected <50 years). Although this risk is lower when probands are affected at an older age (<70 years), their relatives remain to have increased risk for future CAD even after adjustment for classic risk factors (hazard ratio 1.7 (95% CI 1.5 -1.8)).

Taken into account all studies in the systematic review, there remains a significant hiatus in current knowledge concerning family history: there is no data available for individuals with a proband affected before the age of 45 years. The studies with the lowest age criteria for family history set these at “before the age of 50 years”. Therefore, is it unknown what this practically means for risk assessment in relatives of probands affected at the age of 30 years. We would recommend that the limited data of young affected probands from the prospective cohorts becomes available so it can be pooled for a meta-analysis.

Furthermore, we identified definitions of a family history of premature CAD used in various risk score algorithms and guideline documents and validated these according to literature. We found that there are two definitions of a family history of premature CAD used (all relatives <60 years; or male relatives <55 years, female relatives <65 years) and that these increase cardiovascular risk approximately two-fold. These definitions seem randomly chosen. Despite the lack of
uniform criteria, one can argue that a randomly chosen definition of a positive family history is still a valuable asset for risk stratification. However, the danger of not having a uniform definition for ‘premature’ CAD may give rise to confusion amongst clinicians, which translates into underutilisation of a family history of premature CAD during cardiovascular risk stratification.

Chapter 3 describes a retrospective cohort study in 275 patients with premature CVD. Since premature CVD and CVD at advanced age differ in phenotype and contribution of risk factors, it is possible that other - possibly genetic - mechanisms may underlie premature CVD, for which current prevention strategies might not be targeted for. Considering the genetic component, it was tested in this cohort whether patients with premature CVD and a family history of premature CVD had an increased risk for recurrent cardiovascular events, compared to those without a family history of CVD.

It was found that patients with a family history of premature CVD have a 30% increased risk for recurrent cardiovascular events during follow up, independent of treatment. This implies that specific pathophysiological mechanisms are of importance in these young patients in which standard medical treatment is currently not targeted for.

Chapter 4 is an extension to chapter 3. Since the cohort used in the former chapter consisted of a limited number of patients, we tried to confirm and extend our findings in a larger cohort, consisting of 3,102 patients with premature CAD.

We collected retrospective data from all consecutive patients who presented with a first and premature CAD event at the coronary care unit of the Academic Medical Center in Amsterdam. Premature CAD was defined as an event occurring before the age of 51 years in men and 56 years in women. After a mean follow-up of 6.1 ± 3.7 years, 1,027 patients had a recurrent event. Patients with recurrent events had more often a family history of premature CVD compared to those without recurrent events (60.4% vs. 46.7%). After adjustment for cardiovascular risk factors and differences in pharmaceutical treatment, we found that patients with a family history of premature CVD had an increased risk of recurrent CAD events (hazard ratio 1.45 (95% CI 1.12-1.98)). This implies that additional pathophysiological mechanisms are of importance in these young patients that might not be corrected by current medication. Therefore, these patients might be included in the current guidelines for more aggressive treatment.

In chapter 5, an additional analysis was performed in the cohort described in chapter 3. Since it was found that a family history of premature CVD was associated with recurrent cardiovascular events, we explored whether this was associated with a specific type of event. Recent studies have shown that premature CVD is associated with coagulation abnormalities. Therefore, the cohort was stratified according to the type of first event: an acute thrombotic or a stable atherosclerotic event. Furthermore, a thrombin generation test was performed to analyse a possible prothrombotic phenotype in the patients.
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It was found that in patients with a first acute thrombotic event, a family history of premature CVD was associated with a four times increased risk for a recurrent thrombotic event compared to patients with a negative family history. In contrast, a family history of premature CVD was not associated with an increased risk for a recurrent stable atherosclerosis. Moreover, it was found that those with acute thrombotic events have the highest thrombin generation. Therefore, within such families, specific prothrombotic mechanisms - leading to arterial thrombotic events - may be responsible for the premature CVD.

Part II: Risk stratification in families with premature coronary artery disease

For chapter 6 we have reviewed recent literature on carotid intima-media thickness, flow mediated dilation, coronary artery calcification (CAC) and nuclear myocardial perfusion imaging and their ability to individualize risk assessment in families with premature CAD. Generally, literature shows that those with a family history of premature CAD have increased propensity towards subclinical atherosclerotic disease. We conclude that although CAC scoring holds the best promise for risk discrimination within families with premature CAD, more research in this field is urgently needed.

In chapter 7, a novel method to assess microvascular function was explored. The traditional risk score algorithms poorly predict cardiovascular risk in general, but even more in relatives of patients with premature CAD. Therefore, investigators keep on searching for practical tools for assessing subclinical disease, to identify subjects with early onset CAD. We performed a case-control study in 50 patients with premature CAD (men affected before 41 years, women before 46 years), 50 of their first degree relatives (FDRs) and 50 healthy controls. Furthermore, the FDRs were divided into two groups according to the results of their CAC score. We visualized the sublingual microvasculature via videomicroscopy. More specifically, we were interested in the perfused boundary region. An increased perfused boundary region represents deeper penetration of erythrocytes towards the endothelium, which are normally shielded from the endothelium by a cell excluding, protective layer. This cell excluding layer was originally observed in intravital microscopy studies of muscle microcirculation in rodents and later confirmed in studies involving humans. As expected, it was found that the perfused boundary region was increased in patients with premature CAD compared to controls. Furthermore, it was found that the FDRs had an increased perfused boundary region, independent of other risk factors, compared to the controls. Interestingly, FDRs with elevated CAC score also had an increased perfused boundary region, while this accounted not for FDRs with normal CAC score. This means that the increased cardiovascular risk in relatives of patients with premature CAD is influenced by local microvascular dysfunction. Taking into account the non-invasive nature of this imaging method and the easy applicability, this method holds promise for the future, in which identification of microvascular dysfunction is an interesting target for early risk prediction within families with premature CAD.
For chapter 8 we focused on the role of arterial stiffness in families with premature CAD. A family history of premature CAD is a risk factor for cardiovascular events and identifies high risk families. However, whereas a family history of CAD identifies whole families at risk, it fails to identify which specific individual is at risk within the family. This emphasizes the need to further refine risk among siblings in these families. Pulse wave velocity (PWV), the gold standard of arterial stiffness, has emerged as a novel biomarker for predicting cardiovascular mortality and morbidity, independent from traditional cardiovascular risk factors. Furthermore, it was recently found in a prospective trial that PWV measurement could be particularly useful in younger individuals with a genetic predisposition for CAD. However, it is unknown whether families with premature CAD have increased PWV. Therefore, we assessed in a case-control design PWV in patients with premature CAD (men affected before 41 years, women before 46 years), their FDRs and healthy controls.

We found that patients with premature CAD had increased PWV compared to their FDRs and controls. More important, we found that the FDRs also had increased PWV compared to controls, independently of other cardiovascular risk factors. This holds promise for the future, in which arterial stiffness could play a role in risk prediction within families with premature CAD. However, to be able to evaluate the prognostic value of PWV, prospective studies in families with premature CAD are needed.

Chapter 9 addresses the utility of CAC scoring in risk stratification among families with premature CAD. Again, in this chapter we obtained to find a method for improving risk assessment among families with premature CAD. As such, CAC has emerged as tool for the prognostic evaluation of CAD risk. In fact, prospective follow-up studies have shown that CAC predicts cardiovascular events, independent of other risk factors. Recent studies show that determining CAC on top of established cardiovascular risk algorithms, results in a net reclassification improvement ranging from 14% to 30%. Hence, assessing CAC scores in families with premature CAD might help in the decision who should receive treatment and who should not. In a cross-sectional study, we explored the distribution of CAC scores among 265 individuals with and 265 individuals without a family history of premature CAD. We found that those with a family history of premature CAD had increased risk for elevated CAC scores, even after adjustment for traditional risk factors. In a prospective cohort study, we performed a post-hoc analysis on the database of the St. Francis Heart Study. All individuals with a CAC score of zero (n=318) and a CAC score above the 80th percentile (n=512) were analyzed separately, stratified to family history. Subsequently, it was assessed whether a family history of premature CAD was associated with an increased risk of cardiovascular events during follow-up in both groups. It was found that after 3.5 years follow-up, in those without CAC, event rate was equally low in those with (0%) and without (1%) a family history of premature CAD. However, for those with an elevated CAC score, individuals with a family history of premature CAD had increased risk for cardiovascular events (12.5%) compared to those without a family history of premature CAD (6.8%). These findings imply that adding CAC score to family history has capacity to identify individuals at increased risk for future cardiovascular disease in high risk families.
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Chapter 10 is a further extension to chapter 9. In the former chapter we showed that increased CAC score in those with a family history of premature CAD leads to an increased risk for future cardiovascular events. However, it is unknown whether medical treatment might reduce cardiovascular events in this population. Therefore, we performed a post-hoc analysis on the St. Francis Heart Study Randomized Clinical Trial, which assessed the efficacy of treatment with atorvastatin 20mg in healthy, asymptomatic individuals with a CAC score above the 80th percentile for age and sex, compared to placebo. The original trial showed a decrease in cardiovascular events, which failed to meet accepted levels of significance. In the post-hoc analysis, the original cohort was stratified to family history. We found that for individuals with a CAC score above the 80th percentile, after 4.3 years of follow-up, in those with a family history of premature CAD, treatment with atorvastatin lead to a 45% reduction in cardiovascular events, compared to placebo. In individuals without a family history, there was no effect of treatment with atorvastatin compared to placebo. These results have important implications for future guidelines concerning primary prevention in individuals with a family history of premature CAD. Although much controversy exists with regard to treatment of those with elevated CAC score in primary prevention, preventive treatment of individuals with a family history of premature CAD and a high CAC score could indeed be beneficial in terms of cardiovascular outcome.

PERSPECTIVES

In spite of the fact that a family history of premature CVD and CAD has been widely accepted as independent risk factor for cardiovascular events, there is a need for more research in this field in view of the lack of implementation of family screening in clinical practice. In this thesis, patients with premature CVD or CAD and with a family history of CVD were found to have increased cardiovascular risk, despite adequate treatment. Although this was assessed retrospectively, these results could be confirmed in multiple cohorts. This specific finding needs further prospective evaluation, prior to amending the guidelines on cardiovascular prevention. However, there are clear indications that residual risk remains high in these patients and that they are therefore not sufficiently protected against future events. After these findings will have been confirmed, a new goal will be to establish which strategy needs to be implemented to decrease that risk. With regard to FDRs of patients with premature CAD, more studies are warranted to investigate risk stratification in this specific group. We found an inverse relation between the associated risk increase for relatives and the age of onset of a CAD event within the family. However, there is no data available concerning probands affected before the age of 45 years, which is a hiatus in current knowledge on family history. We also found that the current risk score algorithms and guideline documents use different criteria to define a family history as “positive”, which seem randomly chosen. This may give rise to confusion amongst clinicians, which translates into underutilization of the use of a family history of premature CAD during cardiovascular risk stratification. The results in this thesis suggest that FDRs could be divided in a low-risk and a high-risk subgroup. Identification of latent atherosclerotic disease can help to identify high-risk individuals within these families, which may help to guide primary prevention.
strategies. Before this can be established, there is need of several hurdles to be taken. First of all, it needs to be determined if imaging modalities are suitable to guide therapeutic decisions on an individual level in high-risk families in a cost effective way. In order to establish this, a prospective observational trial is urgently needed. One can think of cIMT, CAC scoring and carotid MRI as modalities to be used. Second, a large scale outcome trial is required to evaluate the use of preventive pharmaceutical interventions in patients with advanced subclinical atherosclerosis. Due to the disappointing failure to reach statistical significance in the St. Francis Heart Study Randomized Clinical Trial [1] - the only randomized clinical hard outcome trial based on subclinical atherosclerosis - the verdict is still out for CAC scoring as recommendation for preventive pharmaceutical therapy in the general population. In this thesis we have demonstrated that it is advised to use CAC scoring in families with premature CAD to guide statin treatment. However, this promising subgroup analyses deserves confirmation for the general population. Although some do not see the added value of such a laborious trial, this is heavily disputed by others [2]. Furthermore, it should not be forgotten that within the use of current guidelines and recommendations, much is to be gained. A systematic review [3] recently highlighted that FDRs of patients with premature CAD do not recognize heredity as cardiovascular risk factor, underestimate their own cardiovascular risk, are not adequately treated for their risk factors and are neglected in preventive screening programs, hereby ignoring guidelines. Although current guidelines concerning families with premature CVD or CAD need improvement, an imperfect guideline is better than no guideline at all. Therefore, it is important for clinicians to be adherent to current guidelines and use these properly. To render clear recommendations from the abovementioned perspectives, I will concisely state my thoughts for what is needed in this research field, hereby not only describing what is known to date, but also to establish future research in the field of family history.

Recommendations for future research:

- Perform a meta-analysis on the limited data of young affected (before the age of 45 and earlier) probands to assess risk in their relatives
- Come to one definition of a family history of premature CVD/CAD in risk score algorithms and guideline documents, enabling proper use of a family history during cardiovascular risk assessment
- Prospectively assess if patients with proven CVD/CAD and with a family history of CVD have increased risk for recurrent cardiovascular events
- If so, evaluate if they benefit from more aggressive pharmaceutical therapy, such as statin treatment
- Prospectively assess if imaging modalities are suitable to guide therapeutic decisions in high-risk families
- Perform a randomized controlled trial to evaluate the use of preventive interventions in those with advanced subclinical atherosclerosis, CAC in particular

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REFERENCES