Heart disease in women and men

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CHAPTER 11

General discussion and future perspectives

GENERAL DISCUSSION

In the first part of this thesis an epidemiological overview of the occurrence of CVD, cardiovascular risk factors and the deficiencies in preventive medication use in men and women of the northern part of the Netherlands was given. Also, resting heart rate as causal risk factor for coronary artery disease and MI was explored. In the second part, the ECG was used for detecting unrecognized MI in the general population. Sex-specific occurrence of unrecognized MI was described as well as its predictors and related symptoms. It was determined whether unrecognized MI is linked to mortality. In the third part, the performance of ECG criteria for detecting LVH was studied in men and women and new sex-specific ECG-LVH criteria were generated. Finally, causal relationships between cardiovascular risk factors and LVH and between LVH and longevity were explored.

Part I: Prevalence and prevention of cardiovascular disease and risk factors

Chapter 2 gave an epidemiological overview of CVD and its (untreated) risk factors in the northern part of the Netherlands. Nine percent of the individuals under 65 years of age had one or more CVD and 28% of the individuals aged 65 years and over. Almost three out of four individuals had one or more cardiovascular risk factors. These values are representative for the rest of the population of the Netherlands[1]. The reported prevalence of CVD and cardiovascular risk factors are similar to reports of the World Health Organization on the Netherlands[2].

In the Netherlands, decreasing mortality rates of CVD are described[3]. This decrease is partly driven by the improvements in treatment of CVD, for example by the development of reperfusion therapy and antiplatelet agents[4]. Also, favourable trends in systolic blood pressure and total cholesterol levels and a decreasing prevalence of smoking and physical inactivity contributed to the decrease in CVD mortality[5]. The current reported prevalence of CVD and cardiovascular risk factors in the contemporary population suggest, however, that the burden of CVD is still high. Also, prevalence of obesity and diabetes is still increasing in the contemporary Dutch population[5]. This unfavourable trend in BMI, is seen in children as well[6]. One out of seven children in the northern part of The Netherlands are overweight or obese (this thesis). In children and adolescents, overweight and obesity cluster together with other cardiovascular risk factors[7], placing them at high individual risk for future CVD, but also potentially increasing the future economic burden of health care costs[8]. In addition, individuals who develop CVD nowadays tend to live longer, resulting in a relative morbidity expansion[9]. Reducing

the expected burden of CVD can be pursued by both preventive medication use and by health campaigns promoting a healthy lifestyle. As reported in chapter 2, the number of individuals without preventive medication use is substantial and has been reported before[10]. Additionally, when individuals do receive cardiovascular preventive medication, only half of them achieve the treatment goals[11]. Chapter 3 focused on the recommendations for preventive medication use according to CVD prevention guidelines of the ESC and NHG. These recommendations are based on the SCORE risk estimates for calculating ten-year CVD mortality risk[12]. It has been described that this estimation seriously underestimates overall cardiovascular risk, particularly in younger age groups and women[13]. The number of untreated individuals who are at high CVD risk, may thus even be higher than reported in this chapter. During or before the Lifelines baseline visit, around one third of the individuals at risk received blood pressure or lipid lowering medication. After giving feedback of an individual's cardiovascular risk profile through the Lifelines assessment, prevalence of preventive medication use almost doubled. Nevertheless, approximately one third of the individuals at risk still not received preventive medication. Motivation and attitude toward preventive medication use of both patient and general practitioner may play a role here and also highlights the importance of promoting healthy lifestyle to reduce the prevalence of cardiovascular risk factors[14].

Dutch health campaigns are nowadays not able to change people's lifestyles; and more aggressive initiatives should be undertaken to decrease the prevalence of cardiovascular risk factors. A large five-year mass media campaign (2002-2007) on overweight and physical activity in the Netherlands showed that despite the high levels of publicity and campaign exposure, the effect was not strong enough to provoke substantial changes in important predictors of behaviour change[15]. In 2005, the Netherlands signed the WHO Framework Convention on Tobacco Control (FCTC) to strive for a smoke free society, but a lot of goals set by the FCTC are still not met[16]. That such imperative health programmes can be effective in reducing the number of individuals at risk is demonstrated in other countries[17]. As an example, the "North Karelia Project" in Finland successfully reduced the prevalence of cardiovascular risk factors through media campaigns, community meetings, chats in people's kitchens, and village-versus-village competitions over cutting back on smoking or reducing cholesterol[18]. The changes in risk factors explained over 70% of the very large observed declines in CVD mortality between 1982 and 1997, while medical treatments explained only 23%[19]. In the United States, the Office on Smoking and Health, a governmental health programme, actively discourages smoking. Nowadays, smoking rates are much lower in the United States as compared to the reported values in the Netherlands[20]. The United Kingdom initiated a nationwide salt reduction programme in 2003 and 2004. Observed declines in blood pressure at

population-level are larger in the United Kingdom than in the Netherlands[21]. Lastly, taxes on sugar-sweetened beverages in the United Kingdom and Mexico are expected to reduce the burden of obesity and obesity related diseases in those countries[22,23].

With the current National Prevention Accord, the Dutch government aims to achieve a 100% smoke-free generation and reduce adult smoking prevalence to five by 2040[24]. Other ambitions of the Dutch government are to turn the expected increase of more than 60% overweight in 2040 to decrease to less than 40% and to decrease the percentage of problem drinkers from 9 to 5%[24]. Hopefully, these more aggressive strategies will result in favourable trends in cardiovascular risk factors and lifestyle; not only for health on an individual level, but also for the economic burden nationwide[24].

Chapter 4 gave an overview of population based ECG values in the Lifelines population; the most recent, and detailed large data source of a Caucasian population with available 12-lead ECG of all participants. An extensive overview was given of sex- and age-specific ranges of heart rate, P wave and QRS complex durations and PQ and QTc intervals in a population free of CVD. The prevalence of ECG abnormalities was described as well. These analyses underline that age and sex should be taken into account in the evaluation of the ECG. In chapter 5, resting heart rate as causal risk factor for coronary artery disease and MI was explored. Resting heart rate has been associated with CVD in observational studies[25]. However, resting heart rate is influenced by a plethora of mechanisms, which could all confound the association with CVD. Genetic analyses have the potential to overcome this source of bias. Genetic variants (associated with resting heart rate) are randomly assigned when passed from parents to offspring and are therefore mostly unrelated to the presence of confounders. In a GWAS meta-analysis, performed in 835,465 individuals, 493 genetic loci associated with resting heart rate were identified, of which 276 were novel. Using all 493 genetic loci in MR analyses, did not show any causal links between resting heart rate and coronary artery disease and MI. Higher resting heart rate is thought to be a marker of an imbalance between the parasympathetic and orthosympathetic system and may therefore be a marker of overall well-being rather than a marker of cardiovascular health. Resting heart rate can increase independently of the genetic profile of resting heart rate due to several influential and non-influential factors, such as obesity and stress[26,27]. Since no relationship between genetically determined resting heart rate and CVD was identified, this link could likely be explained by acquiring a higher resting heart rate during life.

Part II: Unrecognized myocardial infarction

Part II emphasizes that primary prevention and early detection need to be improved. In chapter 6, the prevalence of unrecognized MI was described in 152,180 individuals

of the northern part of the Netherlands who participated in the Lifelines Cohort study. Unrecognized MI was defined when a participant had ECG signs corresponding to a prior MI without a self-reported history of MI. During a median follow-up period of five years, unrecognized MI was independently associated with mortality. In chapter 7, the incidence rate of unrecognized MI was determined in 97,203 Lifelines participants with available follow-up data including an ECG. This incidence rate might be a more accurate measure than the prevalence since new ECG changes could be identified in individuals with a normal baseline ECG. Classical cardiovascular risk factors as hypertension and smoking, were predictors of unrecognized MI and self-reported (cardiopulmonary) symptoms were less often described by individuals with unrecognized MI compared to individuals with recognized MI.

Overall prevalence and incidence rate of both recognized and unrecognized MI were higher in men compared to women and increased with older age; findings that do not appear to have changed over time[28]. However, the consistently higher reported proportion of unrecognized MI in women compared to men, suggests that women are at increased risk for not recognizing MI and for the associated burden of unrecognized MI. It has been described that lower pain sensitivity is more strongly associated with unrecognized MI in women than in men and may therefore be one of the explanations for the higher proportion of unrecognized MI among women[29]. Attitude of patients and general practitioners towards cardiovascular risk may also influence perception of pain and symptoms. Women less often relate their chest pain to cardiac disease compared to men[30]. Also, public information and medical training of health professionals have mainly focused on recognition of male pattern symptoms, leaving women at greater risk. Currently, the impact of CVD on the health status of women is gaining more recognition and becomes a focus of public education efforts such as the "Go Red for Women" campaign sponsored by the American Heart Association[31]. In the Netherlands, among others, the "Netherlands Heart Foundation" pays attention to CVD in women[32] and more and more research is performed on the female heart. However, many gaps are not filled yet and further research is needed to increase knowledge on sex-differences in cardiac pathology and linked personalized detection and prevention of CVD.

As described in chapter 6 and 7, similar risk factors were associated with unrecognized and recognized MI and suggest shared etiology. The importance of early identification of cardiovascular risk factors is borne out once more by these observations and may be of particular interest for subgroups at risk, including women. The proportion of unrecognized MI might be reduced by a systematic risk assessment in intermediate and high risk patient groups. It has been reported in a systematic review that systematic screening for cardiovascular risk factors had no effect on mortality, coronary heart

disease and stroke[33], but only limited data was available. In the same review, there were some favourable effects described on cardiovascular risk factors through risk assessment, suggesting the need for follow-up studies focused on early detection of cardiovascular risk. The sensitivity of the ECG for diagnosing old MI is low and lies between 0.30 and 0.58[34]. However, the sensitivity and possible benefits of the ECG may be higher for diagnosing incident unrecognized MI in a population with an available reference ECG. Besides screening for cardiovascular risk factors, further research is needed to determine the benefits of ECG or cardiovascular imaging studies in primary prevention and/or screening for unrecognized MI.

Part III: Left ventricular hypertrophy

In chapter 8, the accuracy of the ECG in detecting LVH was described. The sensitivity of the ECG for predicting LVH is low, especially in women. The increased cardiac morbidity and mortality associated with LVH supports the need for sex-specific ECG criteria to achieve optimal performance for the detection of LVH. Currently used ECG-LVH criteria were developed many decades ago in special populations that are not representative for the current general population[35,36,37]. Sex differences on the ECG are well described and suggest sex-specific ECG criteria or cut-off values for predicting LVH as well[38]. Using imaging data of the recent UK Biobank imaging study, with available cardiac magnetic resonance imaging (CMR) and 12-lead ECG data of around 3,600 individuals, sex-specific ECG criteria for detecting LVH were developed, with similar sensitivity for men and women. The developed ECG-LVH criteria are the first that were generated with CMR data. CMR provides most accurate and reproducible estimates of left ventricular mass[39] and therefore represents the gold standard.

Previous studies showed an association between cardiovascular risk factors as obesity, high blood pressure, smoking, hypercholesterolemia and diabetes, with LVH[40], but do not provide sufficient evidence for a causal relationship. MR analyses are designed to investigate the causal nature of the relationship between risk factors and outcomes in observational data in the presence of confounding factors[41]. In chapter 9, evidence was found that genetic variants associated with higher blood pressure also confer a higher risk for ECG predicted LVH (measured by QRS amplitudes and duration), using MR analyses. This result emphasizes the importance of cardiovascular risk assessment to decrease the burden of CVD as described in previous parts of this thesis. Interestingly, no causal relationship was identified between genetically predicted QRS duration or amplitudes and longevity. These findings suggest that the reported association between QRS traits and life expectancy (in populations with medical conditions[42]) may have resulted more from (confounding) environmental risk factors than the genetic

component of QRS duration and amplitudes itself. Further, associations between QRS traits and mortality or longevity could very well be driven by extreme cases (such as QRS duration >120ms) that fall out of range of the genetically predicted variation. Currently, more and more genetic variants associated with cardiovascular risk factors are identified, due to increasing sample sizes of large GWAS (meta-analyses). By using these new variants in future MR analyses, statistical power and risk prediction will be improved. As is described in chapter 8, the ECG has a low sensitivity for detecting LVH. However, the wide availability and cost effectiveness of the ECG, makes it possible to measure QRS amplitudes in a large number of individuals with available genetic data, resulting in the current discovery of 52 loci associated with cardiac mass[43]. GWASs that are performed on other "endo-phenotypes" of heart failure and LVH, still have had limited success[44]. For example, GWAS on left ventricular mass measured in a small number of individuals with available imaging data, only yielded several genetic loci, explaining little variance of the phenotype[45]. The population based UK Biobank imaging study is an initiative that will make it possible to identify more genetic variants associated with cardiac function and structure[46]. In chapter 10, out of 5,596 individuals of the UK Biobank imaging study, manual CMR post-processing analyses were performed in 300 individuals with an extreme genetic risk score of systolic blood pressure (150 highest and 150 lowest). Subsequently, MR analyses were performed and provided evidence for causal relationships between systolic blood pressure and increased left ventricular mass and radial strain. These results confirm the results presented in chapter 9.

Future perspectives

As was described in this thesis, primary prevention and detection of CVD is currently suboptimal and new research is essential. Population based screening studies identifying individuals with CVD or individuals at risk, will increase our knowledge on the effect of cardiovascular risk assessment. Examples are the currently performed Dutch population based screening studies Risk or Benefit in Screening for CVD (ROBINSCA)[47] and Early-Synergy. In ROBINSCA, 39,000 participants aged between 55 and 74 years old will be stratified to three groups, comparing no further screening with classical risk management and CT calcium scoring. In Early-Synergy, individuals with a high calcium score, identified during the ROBINSCA study, will be randomized to two groups; one control group and one group of participants who will undergo CMR. Incidence of CVD and mortality will be collected during 5-year follow-up. Other promising research initiatives are the UK Biobank imaging study and the Swedish cardiopulmonary bio-image study (SCAPIS). In the UK Biobank imaging study, 100,000 participants undergo CMR[46]. SCAPIS collects cardiac imaging data of 30,000 men and women[48]. Both initiatives give a unique opportunity to gain further insight in epidemiological characteristics of individuals

with (unrecognized) cardiac disorders or in cardiac function prior to the development of CVD. Such studies will be of high value for improving risk prediction of CVD and for increasing the knowledge on sex differences in cardiac pathology. Additionally, these studies give the opportunity to determine whether ECG or imaging implementation in population screening for detecting cardiac diseases will justify the significant costs. It is also expected that cardiovascular risk prediction will improve enormously by the identification of genetic variants associated with cardiovascular risk factors and CVD. Through collaboration and genetic data sharing, genetic studies of CVD now allow genetic risk scores that predict future diseases as good as traditional risk factors[49]. It is expected that these genetic risk scores will be incorporated in traditional risk scores and will be used more and more in clinical practice. The interplay between genetic and lifestyle risk factors will be a field of interest as well, since it has been reported that an adherence to a healthy lifestyle is associated with a substantially reduced risk of coronary artery disease independent of genetic risk[50]. The UK Biobank is an example of an extensive genomic database including genetic data of 500,000 individuals, that makes it possible to identify more genes related to cardiovascular traits and allows more precise individual risk prediction for CVD. Nonetheless, primary prevention, in terms of improving lifestyle, will remain the most important key in reducing the burden of CVD. The government has a role to play there. Population-wide interventions focused on lifestyle determinants could produce large, rapid and cost saving benefits.

CONCLUSION

In this thesis, it was described that primary prevention and detection of CVD is currently suboptimal. In the northern part of the Netherlands, the number of individuals with cardiovascular risk factors and CVD is high and cardiovascular risk management is being underutilized. It was demonstrated that women are at higher risk for not detecting CVD. In women, the proportion of MIs that remain unrecognized is higher compared to men and ECG criteria for detecting LVH show lower accuracy in women. New sex-specific ECG-LVH criteria, with similar accuracy in men and women, were suggested. Exploring (novel) risk factors of CVD, established evidence for a causal relationship between blood pressure and LVH, but not between resting heart rate and coronary artery disease and MI.

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