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Chapter 1
General introduction
GENERAL INTRODUCTION

The last decades, tremendous progress has been made in improving treatment, and thereby prognosis, of patients with cardiovascular disease (CVD). Several breakthroughs in CVD management and prevention include the introduction of percutaneous coronary interventions in 1979\(^1\) and the introduction of aspirin and cholesterol lowering with statins for treatment of CVD, both in the 1980s.\(^2,3\) Despite this all, CVD remains a primary cause of morbidity and mortality in the western world. In the 2012 update of the heart disease and stroke statistics,\(^4\) it was estimated that the prevalence of CVD in the United States in 2008 was 82.6 million individuals. Each year 785,000 Americans will have a new coronary event and approximately 470,000 will have a recurrent attack. In addition, 795,000 people will have a new or recurrent stroke each year. The 2008 overall rate of CVD death was 245 per 100,000 individuals. Although these numbers are somewhat better in the Netherlands,\(^5\) also there the CVD burden is troublesome, indicating that we have a long road ahead of further improving the available treatment modalities and developing new and better treatment options and preventive measures.

Research on CVD has taught us a long time ago that disease development is an interplay of both genetic and environmental factors. In order to develop new treatment modalities, it is of paramount importance that we further increase our knowledge of the exact biological mechanisms and the genetic background of CVD. However, the multifactorial nature of CVD complicates the interpretation of genetic associations. Although many genetic factors have been associated with the different aspects of CVD, consistent replication has proven difficult.\(^6-9\) The reported genetic factors have small effect sizes and, even taken together, only explain a minor part of the suspected genetic component of the disease.\(^10,11\) This so called missing heritability has puzzled the scientific field and encouraged development of improved genotyping methods and data analysis possibilities.\(^12,13\) First it was only possible to determine one single nucleotide polymorphism (SNP) at a time. Therefore, research focused on candidate genes that were hypothesized to be involved in the disease.\(^14\) Examples of this approach include the angiotensin-converting enzyme gene,\(^15\) the platelet glycoprotein IIIa gene\(^16\) and the matrix metalloproteinase 3 gene.\(^17\) This candidate gene approach was taken to a higher level when it became possible to genotype multiple SNPs at a time on so called multiplexes. After completion of the Human Genome Project\(^18\) and the HapMap project\(^19\) it became evident that SNPs were present in large quantities spread across the genome. In 2005 a new technique became available that enabled simultaneous genotyping of thousands of SNPs. This led to the development of genome-wide association studies, in which exploration of large amounts of common SNPs (>100,000) across the whole genome became possible.\(^20\) Since no prior biologic knowledge was needed for these types of analyses, new unforeseen risk loci could be identified, possibly leading to better
understanding of the disease in question and potentially resulting in novel treatment targets. However, this hypothesis-free approach soon proved to bring along new difficulties as well, since most identified loci were intergenic or even located in gene-deserts and therefore had unclear functions. This biological relevance item is currently the issue most studies try to resolve.

In the current thesis, several aspects of the above described development will be addressed. The first and second part of the thesis will focus on elucidating the genetic background of coronary restenosis and other aspects of CVD using candidate genes approaches, GWAS and post-GWAS analyses. The third and last part of this thesis will address the more clinical side of genetic research, pharmacogenetics. Pharmacogenetics, focusses on the genetic determinants of response to drug therapy with the ultimate goal of applying personalized medicine.

OUTLINE OF THIS THESIS

Part I – Genetics of coronary restenosis

Since its introduction, PCI has become widely accepted as an effective and safe treatment modality for single vessel and multi-vessel coronary atherosclerotic disease. However, an important drawback of PCI is the renarrowing of the treated vessel, resulting in renewed symptoms and the need for repeat intervention. This phenomenon is called restenosis and it is an important cause of morbidity and possibly even mortality after PCI. Restenosis is a complex disease for which the causative mechanisms have not yet been fully identified. In part 1, the genetic determinants of restenosis and the long-term consequences of this disease are explored.

In chapter 2 and chapter 3 an extensive overview of the current knowledge of restenosis is given. In chapter 2 the different mechanisms involved in the development of restenosis are discussed together with the known clinical, biological and procedural risk factors contributing to the individual risk of restenosis. Chapter 3 provides an overview of the latest innovations of optimizing outcomes of coronary stenting and discusses the available preventive and therapeutic measures of in-stent restenosis.

In chapter 4 we describe the results of the very first GWAS published on restenosis that was performed in the GEnetic DEterminants of Restenosis (GENDER) study population. Follow-up studies of this GWAS data resulted in the other 3 chapters in this part of the thesis. After obtaining the GWAS data, we used this data in chapter 5 to clarify the inconsistent results, reported in literature, on the association of genetic variation in matrix metalloproteinases 2 and 3 and restenosis. Next, in chapter 6 we examine all SNPs in the genomic region of all other previously described candidate genes of restenosis. The aim of this study is to explore whether the joint effect of all these SNPs together
indeed is associated with restenosis, despite all the inconsistent results from previous studies. **Chapter 7** describes the next step in unraveling the genetic background of restenosis. In this study we performed pathway analysis of a wide range of biological pathways, related to the key mechanisms involved in restenosis development, with the aim to identify new additional candidate genes for further research. Finally, in **chapter 8** the 10-year follow-up of the GENDER population is presented. In this chapter we examine whether the development of restenosis has an effect on long-term mortality rate. Moreover, we compare the GENDER study with the general Dutch population to see if patients with coronary artery disease still have a worse outcome, despite all therapeutic advances that were made during the last decade.

**Part II – Genetics of (cardio)vascular diseases**

In this second part of this thesis genetic determinants of two other (cardio)vascular conditions are studied. In **chapter 9** we investigate the possible role of DNA repair mechanisms in CVD development by performing a gene set analysis of DNA repair pathways for their association with the CVD events myocardial infarction and stroke. Besides the GENDER population, we include in this study the 5,244 participants of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study. In **chapter 10** we make a sidestep towards nephrology to study a condition with a likely mechanistic overlap with coronary restenosis, i.e. arteriovenous access failure in hemodialysis patients. We determine a wide range of SNPs in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) population and analyze them for their association with arteriovenous access failure.

**Part III – Pharmacogenetics of cardiovascular diseases**

The fact that not all patients have a similar adequate response to drug therapy poses a major problem in guideline-based clinical practice. Several underlying mechanisms for this aberrant response have been proposed and genetic variation is thought to play a major role. Pharmacogenetics is the field of research that examines genetic variation that influences responses to drug therapy in the individual patient. The ultimate goal of pharmacogenetics is the realization of personalized therapy in which determination of genetic polymorphisms can guide pharmacotherapy to choose agents with the greatest potential for efficacy and the least risk of toxicity. Pharmacogenetics also informs clinicians for dose adaptations to specific drugs in patients with aberrant metabolism.

In the first chapter of the final part of this thesis (**chapter 11**) a comprehensive overview is provided of the available pharmacogenetic evidence of the five major drug classes of cardiovascular diseases; statins, antiplatelet agents, anticoagulants, beta-blockers and angiotensin-converting enzyme inhibitors. In **chapter 12**, the eight best replicated SNPs, related to aspirin- and clopidogrel efficacy, are investigated in a
large population of ST-segment elevation myocardial infarction patients, to see whether their influence on recurrent thrombotic events could also be detected in this real-life unselected patient population.
REFERENCE LIST


