Chapter 1

Introduction and Scope of the Thesis
Introduction

Cardiovascular disease is a global health concern, accounting for 4 million deaths in Europe each year.¹ It is usually characterized by systemic atherosclerosis, which is a process that involves endothelial plaque formation eventually resulting in micro- and macro-vascular complications.² In order to slow down this process and to prevent occurrence of fatal or non-fatal cardiovascular complications, many patients require treatment with one or more drugs. In the past 20 years, several treatments have been proven effective in reducing cardiovascular events and this has resulted in a steady decrease in the incidence of cardiovascular disease.³ However, with an increasing prevalence of obesity in both developed and developing countries, combined with high consumption of salt, alcohol, and fatty foods, a sedentary lifestyle, and ongoing smoking habits, it is questionable whether the achievements in reducing cardiovascular morbidity and mortality can be sustained on the long term. Given these considerations, it is likely that cardiovascular disease will remain a leading cause of death around the world. New innovative treatment strategies are highly recommended to mitigate the burden of this disease and thus an important contribution is expected from the pharmaceutical enterprise.

The safety and efficacy profile of any new drug must be well characterized before marketing authorization can be granted. To demonstrate drug efficacy and safety, complex hard outcome trials of long duration, requiring large human and financial resources, are required. To obtain an impression of the drug’s efficacy and to justify conduction of a hard outcome trial in later stages of drug development, the effect of a drug on a biomarker is often assessed. A biomarker is a characteristic that serves as an indicator of a physiological or pathophysiological process, or as a response to treatment which affects such a process. Risk factors can be considered as biomarkers, however risk factors form a distinguished group because they have a direct causal relationship with cardiovascular disease itself.⁴ Throughout this thesis, the term biomarker is used, without making a distinction whether direct causality with disease is considered. When a drug shows a substantial effect on the biomarker it is developed for (i.e. blood pressure for an
antihypertensive drug or cholesterol for a lipid modifying drug), one expects that the drug delivers cardiovascular protection, and in case of blood pressure or cholesterol, this is sufficient to obtain marketing authorization for widespread clinical application. To verify that the drug is indeed delivering what it is intended to do, hard outcome trials are conducted post-registration. This has been the paradigm during the last decades in cardiovascular drug development.\textsuperscript{5,6}

Although this drug development strategy has resulted in many promising and clinically interesting drugs targeting cardiovascular risk factors, recent trials have shown that the drug does not always confer the intended cardiovascular protection, with some cases drawing media attention. One example is sibutramine, which was launched in 1999 because of its proven weight lowering capacities in the absence of remarkable side effects. However, a few years after registration, excessive cases of hypertension and tachycardia were reported in association with use of sibutramine. Therefore, in 2010, European authorities decided to suspend marketing authorization.\textsuperscript{7} Another example is rosiglitazone. This drug received marketing authorization in 2000 based on its HbA1c lowering effect, which was expected to improve prognosis in patients with type 2 diabetes. However, after its introduction to the market, meta-analyses revealed increased risk of myocardial infarction and heart failure associated with use of rosiglitazone, despite its consistent HbA1c lowering effect. This could be attributed to renal tubular sodium retention leading to excessive extracellular fluid retention and weight gain, which fueled discussions about the safety of rosiglitazone. Eventually, marketing authorization of rosiglitazone was suspended in 2010.\textsuperscript{8,9} Yet another example is torcetrapib. This cholesteryl ester transfer protein inhibitor, high density lipoprotein cholesterol (HDL-C) raising drug, was also prematurely terminated, because a hard outcome trial showed increased rates of cardiovascular events among individuals treated with torcetrapib. Additional investigations revealed that the increased cardiovascular event rate was attributable to a rise in blood pressure as a consequence of increased mineralocorticoid activity, which counteracted the beneficial effect of the drug on HDL-C.\textsuperscript{10-12} A more recent example is another cholesteryl ester transfer protein inhibitor dalcetrapib. This drug was intended to improve outcomes in patient with acute coronary syndrome by raising HDL
cholesterol. Despite increases in HDL cholesterol in participants assigned to
dalcetrapib during the trial, no significant reductions in cardiovascular risk
compared to placebo could be reported. The lack of cardiovascular protection with
dalcetrapib could possibly be explained by increases in C-reactive protein en
systolic blood pressure, which have probably counteracted the beneficial effects of
raised HDL cholesterol.\textsuperscript{13}

These examples teach us that the development and targeting of a drug to
a single biomarker may lead to serious misinterpretations of the actual long-term
treatment effect on cardiovascular morbidity and mortality, with major
consequences for the pharmaceutical industry, society, and individual patients.
These unexpected findings can possibly be explained by the fact that a drug may
affect other parameters than the biomarker of interest alone. In the current drug
development process, these so-called off-target effects are considered as side
effects, which implies less rigorous measurement and reporting. Estimating the
drug effect on cardiovascular morbidity or mortality by only taking the on-target
drug effect into account may be problematic. Firstly, the off-target effects may also
influence long-term cardiovascular protection as shown in Figure 1. Secondly, the
response in the on-target and off-target parameters may be different within and
between individuals. For example, angiotensin receptor blockers are registered for
blood pressure lowering. However, these drugs also decrease albuminuria, which
provide additional long-term cardiovascular protection,\textsuperscript{14-16} although the responses
in blood pressure and albuminuria between individual patients may differ.\textsuperscript{17,18} In
addition, these drugs also affect serum potassium and hemoglobin, which could
offset the beneficial effects on blood pressure and urine albumin excretion.\textsuperscript{19} Thus,
combining the drug effect on multiple biomarkers may be a more rational approach
to estimate drug effects on hard outcomes.

**Scope of the thesis**

A more optimal use of biomarkers may improve the estimation of the long-term
drug efficacy and safety, which has the possibility to decrease the high drug
attrition rates in late stages of drug development and could possibly even prevent market withdrawals of already registered drugs.\textsuperscript{20} The current thesis aims to develop novel methodologies to optimize the use of biomarkers during late phases of drug development. This in order to facilitate drug efficacy evaluation and to remove barriers for drug development. More optimal use of biomarkers during clinical trials can be achieved in at least two ways. Firstly, biomarkers allow for selection of patients in whom a beneficial treatment effect on hard clinical endpoints can be expected. Secondly, drug treatment is intended to change the exposure of the patient to a risk factor in order to slow down a pathophysiological process. For example, antihypertensive treatment is intended to reduce the exposure of the individual to the detrimental effects of high arterial pressure. In this
context, the short-term change in blood pressure, or in a biomarker more generally, can be used as indicators of the likelihood that long-term cardiovascular protection will be established.\textsuperscript{21}

In Chapter 2, we assessed whether renal biomarkers can be used for more accurate identification of individuals at elevated cardiovascular risk. The kidney is a highly perfused organ and changes in its function may reflect early vascular damage. To this end, we investigated the additive value of the renal risk factors urine albumin excretion and estimated glomerular filtration rate on top of the established cardiovascular risk factors in the general population. Results of this study may be of value in improving inclusion/exclusion criteria for clinical trials. In doing so, the drug development process can be more focused on patient groups who benefit most from protective therapy. Chapter 3 gives an overview of drug effects on a panel of biomarkers in patients with type 2 diabetes and evaluates whether changes in biomarkers induced by treatment translate into long-term protection. In Chapter 4, we investigated whether off-target effects of the angiotensin receptor blocker losartan on serum uric acid are associated with cardiovascular risk and whether these effects are valuable in guiding cardiovascular protective therapy. In Chapter 5, we aimed to construct a multiple parameter risk response score, composed of short-term changes in traditional and novel cardiovascular risk factors, in order to give an accurate estimation of the long-term treatment outcome. This analysis was performed in a post-hoc environment using data from already completed clinical trials. Therefore, in Chapter 6, we validated the parameter risk response score by predicting the long-term treatment effect of the novel direct renin inhibitor aliskiren on top of conventional antihypertensive treatment in an on-going study of which the hard outcome result was not available at the time when we performed our estimations.
References


