Introduction

General Introduction and Outline of the Thesis

BACKGROUND

Cardiovascular and renal diseases

Cardiovascular and renal disease are leading causes of morbidity and mortality in the developed world. For a long time, health-care interventions are directed at patients with established cardiovascular or renal disease (e.g. heart failure, diabetic nephropathy) to prevent recurrent events and further disease progression with pharmacotherapeutic agents. For several reasons (e.g. ageing of the population), pharmacotherapeutic intervention to prevent cardiovascular and renal diseases, has become more and more important in the last decades. In this respect, risk-factors such as hypertension, hypercholesterolemia and diabetes are generally treated to decrease the risk of cardiovascular and renal disease.\textsuperscript{1-3} In practice, preventive pharmacotherapeutic treatment is only initiated in those subjects that have visited a health-care professional (e.g. general practitioner) for reasons of complaints, specific symptoms and/or explicitly identified elevated risk. This re-active approach does not specifically identify the generally healthy subjects (no complaints and no symptoms). Therefore, there is still much room for further improvement, despite advances in pharmacotherapy. Elevated albuminuria is an early risk-marker of progressive cardiovascular and renal disease. Active population-based screening for elevated albuminuria has the potential to identify subjects in an early asymptomatic disease stage. Such an active approach allows for identification of generally healthy subjects in an early disease stage rather than treatment of risk-factors in the re-active approach.

Albuminuria

Increased levels of albuminuria, also known as elevated urinary albumin excretion (UAE) is a marker for early cardiovascular and renal functional abnormalities.\textsuperscript{4-6} It has been found in various studies that albuminuria is associated with several cardiovascular and renal risk-factors (e.g. age, gender, blood pressure, cholesterol, glucose, body mass index, smoking).\textsuperscript{7-13} Elevated albuminuria, either micro- (UAE 30-300 mg/day) or macroalbuminuria (UAE ≥300 mg/day), predicts worse cardiovascular and renal outcome in patients with diabetes\textsuperscript{14-20}, hypertension,\textsuperscript{21-24} as well
as in the general population. This predictiveness is even independent of other associated cardiovascular and renal risk-factors. Consequently, some guidelines are now including albuminuria as an additional risk-marker for cardiovascular disease.

**TREATMENT AND SCREENING**

Albuminuria has been shown to be associated with loss of renal function and cardiovascular outcomes. From various studies, evidence exists that decreasing albuminuria is associated with improving cardiovascular and renal outcomes.

Pharmacotherapeutic interventions with angiotensin-converting-enzyme (ACE)-inhibitor or angiotensin receptor blockers (ARB) directed at the Renin Angiotensin Aldosterone System (RAAS) have shown to be effective in decreasing albuminuria and related risk for renal outcomes in diabetic and/or hypertensive patients. Importantly, these agents have been shown to lower albuminuria and renal risk more than might be expected from their blood pressure-lowering effect alone. Comparable benefits of treatment of albuminuria with these RAAS intervening agents were found with respect to cardiovascular outcomes. These results on cardiovascular outcomes were generally based on clinical trials among patients with established cardiovascular disease and hypertension, but also general healthy subjects with elevated microalbuminuria. Though these studies indicate that RAAS treatment is associated with decreases in albuminuria that translate in reduced cardiovascular and renal risk, more research is needed to reveal the exact role of albuminuria and treatment options.

Considering aforementioned, it seems reasonable to point at albuminuria as a potential target to improve cardiovascular and renal outcome by pharmacotherapeutic treatment. In particular, this could involve efficient treatment for albuminuria in those subjects with established risk-profiles as a re-active approach and population-based screening for and (early) treatment of albuminuria as an active approach.

In daily practice treatment guidelines, albuminuria could serve as a potential target for treatment with RAAS intervening agents in patients with diabetes, hypertension or established cardiovascular disease to reduce the number of cardiovascular and/or renal outcomes. Active screening for albuminuria in specific patient populations or even the general population, could also serve as a potential opportunity to prevent cardiovascular and renal outcome with RAAS intervening treatment in an early stage.
HEALTH ECONOMICS & PHARMACOECONOMICS

Cardiovascular and renal disease form an enormous and growing burden to health care budgets in developed countries. Early identification and treatment of subjects with elevated albuminuria that are at risk for developing cardiovascular and renal disease events seems desirable from a health care point of view with long-term gains in terms of averted cardiovascular and renal disease events. Is it therefore also recommendable from a health-economic point of view?

Next to considerations on efficacy, safety and effectiveness, health policy and reimbursement decisions are more and more driven by cost-effectiveness outcomes. In particular, this applies to decisions on reimbursement of new pharmacotherapeutic agents and decisions on the implementation of prevention and screening programs. Nowadays, cost-effectiveness analyses precede final reimbursement decisions for new drugs and are important for decisions on the implementation of new health care programs in the Netherlands. Favourable cost-effectiveness outcomes could result in discussions and policy implications that support reimbursement of drugs or the implementation of prevention programs.

The growing role of health-economic and especially pharmacoeconomic evidence in health care decision-making processes requires valid ‘state-of-the-art’ methodologies\(^43\) and structured guidelines for conducting costing research\(^44\) and pharmacoeconomic research.\(^45\) These guidelines are often (slightly) different between countries due to preference reasons.\(^46\)

Given the fact that population-based screening for and early treatment of albuminuria is expected to be effective, favourable cost-effectiveness of such an intervention could lead to discussions that enhance health policy decisions on active screening for subjects that are at elevated risk for cardiovascular and/or renal disease.\(^47\)

POPULATION

Next to data from several published randomized clinical trials, this thesis will primarily build further on observational data from the PREVEND (Prevention of Renal and Vascular ENdstage Disease) study. Details of the PREVEND study have been presented elsewhere.\(^48\) In summary, the PREVEND study is a large prospective community based (observational) cohort study conducted in the city of Groningen that focuses to study the predictive value of microalbuminuria (UAE ≥30 mg/day) for cardiovascular and renal disease. For this study, in the period 1997 to 1998, all inhabitants of the city of Groningen, the Netherlands, aged between 28 and 75 years, were sent a questionnaire and a vial to collect an early morning urine
sample (N=85,421). Of these subjects, 40,856 responded and sent a vial to a central laboratory where urinary albumin and creatinine concentrations were measured. From this population, a cohort of 8592 individuals enriched for elevated albuminuria was selected. Since baseline screening in 1997/1998, further data is prospectively gathered every 3-4 years. Next to clinical measurements, data are gathered on (i) kidney function; (ii) mortality, inclusive cause of death; (iii) cardiovascular and renal events; and (iv) drug use. Data on drug use was derived through linkage to Dutch pharmacy-dispensing records from IADB.nl.

AIMS OF THE THESIS

In this thesis, different epidemiological and health-economic aspects of preventive treatment in patients at cardiovascular and/or renal disease risk are described. Potential strategies for early identification and treatment of subjects with identified cardiovascular and renal risks are evaluated from a health-economic point of view.

The first part of the thesis entitled “Health-economic findings from clinical trials”, addresses the clinical evidence of the efficacy of treating specific patient populations with RAAS intervening agents. In particular, this part focuses on health-economic outcomes that are based on clinical trial efficacy outcomes. Cost-effectiveness of treating cardiovascular and renal risk-factors can be gathered from existing literature or can be derived by conducting economic analyses based on available efficacy data from clinical trials. In this respect, chapter 1 describes an literature review to determine and compare the cost-effectiveness of different RAAS intervening agents in the specific group of type 2 diabetic patients with nephropathy. Possible implications of these cost-effectiveness outcomes are discussed in the light of more practical issues of health-care decision-making. Secondly, the cost-effectiveness of treatment with RAAS intervening agents is evaluated for different patient groups that are at elevated risk for cardiovascular disease events. These studies are based on using data from three different international randomized clinical trials. In chapter 2 the cost-effectiveness of RAAS intervening treatment with valsartan is calculated for patients with chronic heart failure. Additionally, hospital admissions from this Val-HeFT study are used to describe the pitfalls of judging cost reductions based on skewed distributions data in annex 1. Next, chapter 3 describes the results of an economic analysis based on the LIFE study. This chapter describes the cost-effectiveness analysis for treatment with the RAAS intervening agent losartan for a population of patients with hypertension and left ventricular hypertrophy. In chapter 4 the comparative cost-effectiveness of four different ARBs is estimated based on using both clinical trial and observational data.
The second part of this thesis entitled “Health-economic outcomes for albuminuria screening in ‘real-life’ settings, evaluates the epidemiological and economic rationale for population-based ‘screen-and-treat’ scenarios directed at albuminuria. As previously described, several studies have proven that elevated albuminuria is associated with cardiovascular and renal outcomes. Furthermore, treatment directed at the lowering of albuminuria levels has been shown to result in a reduced cardiovascular and renal risk. In particular, this part of the thesis focuses on two aspects: (i) the population that is most likely to benefit from active screening on and treatment of albuminuria; and (ii) the cost-effectiveness of population-based screening for albuminuria followed by treatment in those found with elevated albuminuria levels. Chapter 5 describes and discusses the potential role of screening for albuminuria in specific patient groups (e.g. type 2 diabetic patients with nephropathy) and opportunities for screening in the general population. To further evaluate the potentials for population-based screening for albuminuria, cost-effectiveness for such an approach is estimated based on data from a clinical trial with generally healthy subjects as described in chapter 6. In previous studies it was not formally tested whether active treatment results in significant higher relative risk reductions in subjects with high versus low albuminuria levels. In chapter 7 is this potential albuminuria-dependent effect analysed and are differences in effectiveness between different blood pressure-lowering agents described based on observational data. Chapter 8 evaluates the cost-effectiveness of different population-based ‘screen-and-treat’ strategies that are directed at albuminuria to early identify subjects at elevated cardiovascular and renal risk.

Finally, the results of this thesis are summarized and discussed in the discussion section. Here, the findings of the thesis are translated into final conclusions and recommendations, including some future perspectives.

References


49. http://www.iadb.nl