Discussion

Summary, Discussion, Conclusion and Future Perspectives

In the last decades, cardiovascular and renal disease have been a leading cause of morbidity and mortality in the developed world resulting in an enormous and growing burden to health-care budgets. Therefore, prevention of cardiovascular disease events and prevention of progression to end-stage renal disease will remain very important. Currently, pharmacotherapeutic treatment to prevent cardiovascular and renal disease is generally initiated in subjects with previous cardiovascular events or confirmed renal disease. Prevention is based on treatment of established risk-factors such as hypertension, hypercholesterolemia and diabetes.\textsuperscript{1-4} These preventive measures are more re-active rather than active insofar that such a re-active approach does not explicitly allow for identification of generally healthy subjects in an early disease stage. From a health-care point of view, it seems desirable to early identify subjects at increased cardiovascular and renal risk, even if they are not symptomatic yet. Elevated albuminuria is more and more recognized as an early predictor of cardiovascular and renal disease in specific patient populations (e.g. diabetes, hypertension) and even in the general population.\textsuperscript{5-8} Next to the re-active approach, in which subjects at risk for or with established cardiovascular and renal disease (history) are treated, it has been suggested that active population-based screening for albuminuria could enable early identification and prevention of cardiovascular and renal diseases.\textsuperscript{9-11} In the long run, these early investments for population-based albuminuria ‘screen-and-treat’ strategies are expected to potentially result in health benefits and cost-savings due to averted cardiovascular and renal diseases. This thesis deals with epidemiological and economic issues that relate to preventive (pharmacotherapeutic) interventions with a specific focus on active screening for albuminuria. This chapter summarizes and discusses the main results, findings and ideas as described in the previous chapters.

Statement of Principle Findings

Part I: Health-Economic Findings from Clinical Trials

Firstly, the available pharmacoeconomic evidence on the (cost-)effectiveness of treatment with angiotensin-receptor-blockers (ARBs) in type 2 diabetic patients with advanced renal disease (overt nephropathy) was reviewed in chapter 1. Here, the aim was to get more insight in the economic impact of the favourable results of ARB treatment from
clinical trials among patients with type 2 diabetes mellitus and overt nephropathy. Within trial analytical Markov model techniques were applied to economically evaluate results from these published trials for the US and European settings. All analyses led to comparable Results: ARBs appear to confer both health gains and considerable cost savings if compared with conventional (non-angiotensin-converting-enzyme(ACE)-inhibitor) therapy. Therefore, ARB therapy could be considered as dominant in both the short-term and on the long run. Furthermore, the economic evaluation of the IRMA-2 study suggested that it would be even more cost-effective (cost-saving) to start ARB treatment in an early stage rather than the stage of overt nephropathy. These early treatment investments seem to result in more health gains and cost-savings if compared to the investment in the later stage of overt nephropathy.

How do these favourable results with ARBs compare to the potential comparable effectiveness of ACE-inhibitors? Although, ACE-inhibitors were found to result in similar effects on renal outcomes if compared with ARBs, pharmacoeconomic analyses are scarce and are generally based on intermediate outcomes. If effects of ACE-inhibitors and ARBs are comparable, costs of these drugs become more important for reimbursement decisions. As the first ACE-inhibitors are now off-patent, cost-considerations would favour the ACE-inhibitors instead of ARBs. Head-to-head clinical trials comparing ARBs versus ACE-inhibitors including all relevant long-term costs and effects for calculating the comparative cost-effectiveness are needed to draw further conclusions.

Chapter 2 demonstrated the economic impact of using valsartan in the treatment of patients with heart failure, based on randomized clinical trial findings derived from the Val-HeFT study. The Val-HeFT study was originally designed to assess the additional benefits of the ARB valsartan over already proven favourable long-term effects on cardiovascular morbidity and mortality of ACE-inhibitors and beta-blockers in patients with heart failure. Valsartan therapy resulted in a statistically significant decrease in hospitalisations found during 23 months of the Val-HeFT study follow-up. For the Netherlands, this decrease in hospitalisations was estimated to result in a significant reduction in average costs for heart failure-related hospitalizations of €617 per patients. Mean total costs for add-on therapy were estimated at €8,810 and €8,841 for valsartan and placebo, respectively, corresponding with estimated annual incremental costs for valsartan of approximately €192. Especially in patients not receiving ACE-inhibitor treatment at baseline, valsartan resulted in a statistically significant reduction in heart failure-related hospitalizations and associated costs and was estimated to be cost-saving. For the Dutch situation, valsartan provided benefits in patients with chronic heart failure for modest costs and was
considered as the dominant treatment strategy in heart failure patients not receiving ACE-inhibitor therapy. These findings are not only interesting for the specific case of valsartan, but also from a more general health-care perspective. In particular, this study shows that a pharmacoeconomic profile should also include downstream costs and savings to obtain a complete economic picture for decisions on health-care budgets.

Another country adaptation study was conducted based on results from the LIFE-study; a clinical trial comparing losartan-based and atenolol-based therapy in patients with hypertension and left-ventricular hypertrophy, with comparable blood pressure control in both arms. Compared with atenolol (beta-blocker), the ARB losartan resulted in a significant reduction in the combined risk of cardiovascular morbidity and mortality (13%, \( P = 0.021 \)) with even a 25% reduction in the risk of stroke (\( P = 0.001 \)). In the economic assessment of the LIFE-study for the Dutch situation, stroke costs were €1,076 lower in the losartan-treated group. After inclusion of medication costs, per patient net incremental direct costs were €51 higher for losartan compared with atenolol. The incremental cost-effectiveness of losartan-based versus atenolol-based treatment was estimated at €864 per life year gained (LYG), which is likely to be accepted following the informal Dutch threshold for accepting pharmacotherapeutic interventions. Next to results from chapter 2, also the economic results of the LIFE-study in chapter 3 show evidence for the importance of downstream costs and savings besides the costs of drugs. Despite the higher treatment costs, the current results favour treatment with ARBs both from a clinical as well as pharmacoeconomic perspective. Though there is even additional evidence in favour of ARBs (e.g. lower risk of onset diabetes, better compliance/persistence), clinical trial evidence is generally gathered within selected patient groups and can therefore not allow for direct extrapolation to the general population in the real-life clinical practice setting. In this respect, it is also important to have information on the comparative cost-effectiveness of different ARBs that are generally expected to be mutually replaceable.

To add to discussions on rational prescribing of antihypertensives in daily practice, a comparative economic analysis for ARBs was conducted based on both clinical trial and observational data. Costs and effects of different ARBs in treating patients with essential hypertension in the Netherlands, were presented in chapter 4. Within-trial observed blood pressures after 8 weeks were applied to an international model to estimate the number of cardiovascular complications and related costs for a hypothetical cohort of 100,000 patients with essential hypertension. Note here, that the model was adapted to the Dutch situation by using Dutch cost-estimates for cardiovascular and cerebrovascular complications. Olmesartan resulted in most cardiovascular/cerebrovascular events and mortality averted after
1 and 5 year(s), and was considered as cheapest agent with lowest net costs (per complication averted). Dutch pharmacy data showed that within-trial dosing was not found in clinical practice. On average olmesartan was dosed below the trial dose, whereas losartan, valsartan and irbesartan were dosed above the trial dose. Notwithstanding considerable decreases in blood pressure with all four ARBs, olmesartan appeared to be the most favourable and cost-efficient option from a pharmacoeconomic point of view. The current results of this comparative clinical trial are difficult to translate into definite recommendations for a real-life setting. Health-care professionals generally aim at blood pressure decreases below a certain threshold which is different from the study design with fixed doses. Moreover, the current results are based on a surrogate endpoint (blood pressure) rather than hard cardiovascular endpoints. In the light of these findings and to obtain definite clinical relevant recommendations, further analyses should be conducted based on head-to-head comparison of ARBs at comparable blood pressure control including hard cardiovascular endpoints.

**Part II: Health-Economic Outcomes for Albuminuria Screening in Real-Life Settings**

As described in Part I, economic outcomes from various studies suggest that treatment with RAAS-intervening agents compared with conventional (non-RAAS) agents result in health gains and favourable cost-effectiveness outcomes. In particular, treatment of patients with type 2 diabetes and nephropathy in the early stage of microalbuminuria compared with late overt nephropathy were found to be more cost-saving. This suggests that early detection and treatment of subjects at elevated risk for progression to end-stage renal disease could be an proper practical and cost-effective tool. As described in the introduction section, albuminuria has not only been shown to be predictive for renal disease progression, but it is also associated with the risk of cardiovascular disease events. In chapter 5 the potentials of screening for microalbuminuria (UAE ≥30 mg/d) and macroalbuminuria (UAE ≥300 mg/l) were discussed. Should we screen for elevated albuminuria in specific patient populations (e.g. type 2 diabetic patients) and/or the general non-diabetic patients? For the specific case of type 2 diabetes patients, universal treatment with ACE-inhibitors was found to be cost-effective in a previous study. Based on indications from the both the PREVEND and PREVEND-IT studies, there are signals that albuminuria-based ‘screen-and-treat’ strategies could be successful in reducing the number of renal and cardiovascular outcomes. Such ‘screen-and-treat’ interventions are likely to be cost-effective, as long as all renal and cardiovascular outcomes and proper cost-estimates are included. In general, cost-considerations are likely to favour the use of the cheaper off-patent ACE-inhibitors instead of ARBs.
The PREVEND-IT, a double-blind randomized, placebo-controlled trial within the PREVEND observational study was conducted to assess the effects of ACE-inhibitor therapy (fosinopril 20 mg) on cardiovascular events in generally healthy subjects (e.g. no hypertension, normal cholesterol levels) with elevated albuminuria (UAE ≥15 mg/d). Subjects who received fosinopril had a significant reduction in albuminuria level and a clinical relevant 40% lower incidence of cardiovascular events than subjects in the placebo group. Chapter 6 presents the results on the cost-effectiveness of using fosinopril for such primary prevention of cardiovascular events in subjects with albuminuria from a Dutch perspective. Based on using within-trial PREVEND-IT data, observational PREVEND data and Dutch cost-estimates, the cost-effectiveness of screening for albuminuria with subsequent ACE-inhibitor treatment in those found positive was estimated at €16,700 per LYG. Stochastic analysis indicated that the probability of the cost-effectiveness being below the suggested informal Dutch threshold of €20,000 per LYG was estimated at 59%. Limiting ACE-inhibitor treatment to only those with albuminuria levels of ≥30 mg/d or ≥50 mg/d resulted in even more favourable cost-effectiveness of €12,000 and €7,000 per LYG, respectively, with increasing threshold probabilities. Also, limiting screening to those subjects aged >50 or >60 years improved the cost-effectiveness considerably. These economic outcomes from a Dutch health-care perspective, are the first to suggest a potential favourable cost-effectiveness of an albuminuria-based ‘screen-and-treat’ program in the general population. Here, the short-term benefits of prevention of more acute cardiovascular events with ACE-inhibitor therapy coincides with delay in renal disease progression in terms of decreases in albuminuria levels and therefore potential long-term prevention of end-stage renal disease.9

In chapter 7 it was investigated whether the efficacy of blood pressure-lowering agents to lower cardiovascular events is dependent on baseline albuminuria level and type of agent. Data from the community based prospective PREVEND cohort study were analyzed to provide answers on these important issues. Blood pressure-lowering agents were found to be effective in ameliorating cardiovascular outcome. Absolute cardiovascular risk reductions with blood pressure-lowering agents, were superior in subjects with higher baseline albuminuria levels. Furthermore, results from Cox proportional hazard regression analyses showed that the relative risk for cardiovascular events after start of blood pressure lowering agents is significantly (P < 0.05) dependent on level of baseline albuminuria. The higher the baseline albuminuria in subjects with hypertension, the more outspoken the relative risk reduction for cardiovascular disease is. Numbers needed to treat to prevent one cardiovascular event were estimated at 154, 17 and 8 for all subjects and those subjects with UAE ≥15 mg/d and UAE ≥30 mg/d, respectively. Though not statistically significant,
the use of ACE-inhibitor/ARB treatment tended to be associated with a more favourable cardiovascular prognosis if compared with non-ACE-inhibitor/ARB treatment. These results based on observational ‘real-life’ have important consequences in suggesting that hypertensive subjects with elevated levels of albuminuria have on average higher risk for cardiovascular events compared with generally lower risk in hypertensive subjects with low albuminuria levels. Furthermore, prescription of blood pressure-lowering agents (especially ACE-inhibitors and ARBs) will result in higher relative and absolute risk reductions in hypertensive subjects with higher elevated albuminuria levels. This in combination with the clinical and economic results from the PREVEND-IT study could serve as a good rationale for a population-based ‘screen-and-treat’ program for the general population.

Various population-based ‘screen-and-treat’ scenarios directed at screening for different thresholds of elevated albuminuria (e.g. microalbuminuria and macroalbuminuria) were economically evaluated in chapter 8, to identify the most favourable cost-effective strategy to prevent both cardiovascular and renal diseases. Here, data were used from the observational PREVEND study, to add to the cost-effectiveness findings based on clinical trial data as described in chapter 6. A multi-state transition Markov model was developed to simulate the ‘natural course’ of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events. In the base-case analysis, cost-effectiveness was calculated based on a two-stage screening of the general population on microalbuminuria (pre-screening on UAC ≥20 mg/l and confirmation-test for treatment with UAE ≥30 mg/d) followed by ACE-inhibitor treatment in those found positive. The per-person difference in net costs for screening and subsequent ACE-inhibitor treatment versus no screening was estimated at €926 (€2,003 versus €1,077). Prevention of cardiovascular death was estimated to gain 0.0421 per person discounted LYG. Following from this, cost-effectiveness of population-based screening for microalbuminuria with subsequent ACE-inhibitor treatment was estimated at €22,000 per LYG in the Netherlands. The probabilities for accepting screening for microalbuminuria for maximum willingness-to-pay thresholds of €20,000, €50,000 and €80,000 per LYG was estimated at 54%, 90% and 95% respectively. Limiting screening to those subjects aged >50 or >60 years resulted in a more favourable cost-effectiveness. These results suggest already favourable cost-effectiveness of screening on microalbuminuria in the general population. In particular, the incremental analysis shows that screening on microalbuminuria is associated with relatively high incremental effects for relatively low additional costs and could therefore be considered as potentially reflecting the most optimal option of the efficiency frontier. Although, it is cost-effective to limit screening to subjects at higher age or to restrict treatment in subjects with
macroalbuminuria, screening and treatment in selected populations is less favourable in terms of absolute numbers of subjects that are identified for potential successful preventive treatment. In particular, active screening for microalbuminuria increases the likelihood that subjects with elevated risk for cardiovascular events and renal disease are identified for receiving successful preventive treatment in an early phase.\textsuperscript{11}

The current analyses presented in Part II of this thesis discuss opportunities for active population-based 'screen-and-treat' scenarios directed at elevated albuminuria. Cost-effectiveness results based on both randomized clinical trial and observational data, indicate that practical implementation of active screening for microalbuminuria in the general population is worthwhile to be considered by health-care decision-makers.

\textbf{What Lessons can be Drawn from the Cost-Effectiveness Analyses?}

Pharmacotherapeutic guidelines, disease severity and cost-considerations, play an important role in the choice of preventive treatment for cardiovascular and renal diseases.\textsuperscript{1-4} In this thesis, cost-effectiveness studies applied in specific patients groups for the Dutch situation indicate that drug costs alone do not provide a sufficient full economic picture for treatment with pharmacotherapeutic agents (here antihypertensives). Especially in the more severe disease areas (e.g. diabetic nephropathy and heart failure), downstream cost-savings are likely to cause that the initially more expensive option of antihypertensive treatment is in the end yet a cost-effective option. ARBs are a rather new class of antihypertensive agents that are generally considered comparable to ACE-inhibitors. However, these two classes of drugs interfere at different stages of the renin-angiotensin system and therefore have at least theoretically different therapeutic and effectiveness profiles. Differences are likely to exist on the level of adverse effect profiles and persistence figures.\textsuperscript{20} Cost-effectiveness analyses for ARBs and ACE-inhibitors are available for a variety of patient groups. As (the first) ACE-inhibitors are now off-patent, cost-considerations seem to be in favour of the cheaper generic ACE-inhibitors. Existing economic evaluations based on clinical trials lack these 'head-to-head' comparisons of ARBs versus ACE-inhibitors. Clinical evidence on the comparative effectiveness is only available from smaller trials or specific patients groups at high cardiovascular and renal risk.\textsuperscript{28-30} Therefore, to provide a full economic picture, there is a need for 'head-to-head' comparison of ARBs and ACE-inhibitors to model all (in)direct costs and effects of these agents. For reimbursement decisions and the development of pharmacotherapeutic guidelines, further clinical and economic evidence is needed to elaborate on the therapeutic value of different antihypertensives, especially ARBs and ACE-inhibitors, in daily
practice. Moreover, optimal antihypertensive therapy is not only important from a patient perspective, but increasingly important from a health-care perspective. In addition to considerations on clinical efficacy, tolerability, and experience with pharmacotherapeutic treatment in daily practice, cost-effectiveness outcomes based on including all (in)direct medical costs, should be considered when developing clinical guidelines. In this respect, the indirect comparison approach could be applied for the specific case of antihypertensive treatment (ARBs versus ACE-inhibitors) in the prevention and treatment of cardiovascular and renal diseases.\textsuperscript{31-33} This will add to general trends towards optimal, evidence-based and also cost-effective use of pharmacotherapeutic agents.

Next to secondary prevention of cardiovascular and renal disease and re-active treatment of cardiovascular and renal risk-factors (e.g. diabetes, hypertension, hypercholesterolemia)\textsuperscript{10}, it has been shown that early identification and treatment of subjects with higher levels of albuminuria – a proven predictor of cardiovascular and renal disease risk\textsuperscript{34-36} – is an effective\textsuperscript{10} and (potentially) cost-effective option to prevent these diseases in an early disease stage.\textsuperscript{9}

As generally acknowledged, it is difficult to generalize efficacy results from clinical trial to ‘real-life’ settings.\textsuperscript{22,37,38} It is always very important to realize here that clinical studies are generally conducted in specific patient populations and that dosing of treatment in the ‘real-life’ setting can be different from within-trial dosing. Therefore, these differences between clinical trial and observational settings are likely to also affect the generalisability of cost-effectiveness outcomes. Given the fact that there are more and more methods to reliably deal with observational data,\textsuperscript{39} it is recommendable to combine both efficacy data from clinical trials with effectiveness data from the observational ‘real-life’ setting to provide clinically relevant recommendations on treatment choices. Ideally, this should also apply to health-economic outcomes, where initial analyses for treatment options are based on (scarce) evidence from clinical trials. In particular, additional data gathering from prospective observational studies could give an extra opportunity to evaluate the cost-effectiveness of (pharmacotherapeutic) interventions for extended time-horizons based on data from heterogeneous ‘real-life’ settings. Due to a lot of uncertainties, it is important for health-care decision-makers to value existing (generally scarce) information from clinical trials to sufficiently base their decisions on. Bayesian decision theory together with analysis of the value of information can be used by health-economic researchers and decision-makers to decide whether or not the evidence from a health-economic evaluation is sufficient for decision-making purposes or if it is necessary to conduct additional research.\textsuperscript{40-42}
WHAT IS THE HEALTH-ECONOMIC PROFILE OF ALBUMINURIA SCREENING IN REAL-LIFE SETTINGS?

Higher levels of albuminuria have proven to be associated with cardiovascular and renal risk-factors as well as with hard cardiovascular and renal outcomes and is considered to be an important target for pharmacotherapeutic intervention with RAAS-intervening agents in subjects with diabetes, hypertension, but also the general population.\(^\text{10}\) The epidemiological and health-economic aspects of treatment in subjects at increased cardiovascular and renal risk due to elevated albuminuria, were studied in this thesis. In particular, identification and treatment of higher levels of albuminuria was found to be effective in specific patient populations and also the general population.\(^\text{12,13,26,43-46}\) As discussed previously in this thesis, active screening for albuminuria in the general ‘healthy’ population gives the opportunity to intervene in an early disease stage, whereas the more re-active approach generally consists of screening those subjects with known diabetes, hypertension, or established cardiovascular or renal disease. Both these approaches could be considered as important tools in the prevention of cardiovascular and renal diseases. It is therefore tempting to include albuminuria as a risk-marker and target for treatment in therapeutic guidelines and to suggest implementation of population-based screening for albuminuria.

This thesis reviews and describes various economic analyses with a specific focus on the cost-effectiveness of albuminuria-based treatment or active screening for albuminuria followed by treatment with RAAS-intervening agents. Existing studies generally based their economic model on the albuminuria-dependent progression to end-stage renal disease.\(^\text{47-49}\) In contrast to this, the economic model could also include data on cardiovascular outcome as was done based on the PREVEND-IT study results, which was found to be cost-effective in this thesis.\(^\text{26}\) It is reasonable from clinical and health-economic point of view to include both long-term cardiovascular and renal outcome for calculating the cost-effectiveness of population-based ‘screen-and-treat’ scenarios that are directed at higher levels of albuminuria.\(^\text{11}\)

In this thesis, population-based screening for albuminuria to prevent both cardiovascular events and renal disease progression in the general population, resulted in favourable cost-effectiveness outcomes for different ‘screen-and-treat’ scenarios. It was also found that the results were even more favourable when applying extended time-horizons. From health-economic point of view, these time-horizons are ideally life-time with including all relevant costs and effects.\(^\text{30}\) Applying these life-time figures is often in contrast with the generally short-term view of health-care decision-
makers. In that perspective, the economic analyses in this thesis included costs and effects for only first events within relatively short follow-up and could therefore be considered as conservative. Furthermore, it could be expected that population-based screening for albuminuria coincides with additional health gains related to potential early identification of patients with undiagnosed diabetes and hypertension. Such effects have not yet been taken into account in the cost-effectiveness studies. Furthermore, it was conservatively assumed that the screening procedure followed the method applied for the PREVEND-study. As described previously, this rather expensive method consisted of measuring albuminuria in a first morning void urine sample by nephelometry.\textsuperscript{27}

**Conclusions**

Based on data from clinical trials it has been shown that treatment with RAAS-intervening agents in subjects at elevated cardiovascular and renal risk is likely to be cost-effective in preventing cardiovascular and/or renal diseases. Several studies in this thesis emphasize the importance of combining both clinical trial as well as observational data to support evidence-based decisions on health-care interventions and use of pharmacotherapeutic agents.

Furthermore, the analyses in this thesis suggest potential favourable cost-effectiveness of active screening for (micro)albuminuria in the general population. These results were based on both data from clinical trials and observational data, and are therefore likely to be representative for ‘real-life’ settings.

Altogether, the results from this thesis ideally lead to increased awareness of the impact of albuminuria in clinical practice and offer health-care decision-makers tools to seriously consider implementation of a population-based screening that is directed at albuminuria.

**References**

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