Summary

In the last decades, cardiovascular and renal disease are leading causes of morbidity and mortality in the developed world resulting in enormous and growing burdens for 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 is generally initiated in subjects with previous cardiovascular events or confirmed renal disease (secondary prevention). This re-active approach does not specifically identify the generally healthy subjects and is based on treatment of established risk-factors (e.g. hypertension, hypercholesterolemia, diabetes). 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. Next to the re-active approach, it has been suggested that active population-based screening for albuminuria could enable early identification and prevention of cardiovascular and renal disease. This thesis evaluated different epidemiological and health-economic aspects of preventive interventions in patients at increased cardiovascular and renal risk. The first part of the thesis entitled “health-economic findings from clinical trials”, addresses the clinical and economic evidence of treating specific patient populations with renin angiotensin aldosterone system (RAAS) intervening agents. 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.

Pharmacotherapeutic guidelines, disease severity and cost considerations play an important role in the choice of (preventive) treatment for cardiovascular and renal diseases. Cost-effectiveness studies in specific patient groups based on data from clinical trials applied to the Dutch context (e.g. RENAAL, Val-HeFT, LIFE), indicate that drug costs alone do not provide a sufficient full economic picture for treatment with pharmacotherapeutic agents, such as antihypertensives (chapter 1-4). 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 a potentially cost-effective option. One of the aspects discussed here, was the choice of treatment that relates to the scarce availability of comparative effectiveness and cost-effectiveness data for RAAS intervening agents, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE-)inhibitors (chapter 1). As ACE-inhibitors are now off-patent, cost-
considerations seem to be in favour of the cheaper generic ACE-inhibitors. Therefore, the complete economic picture requires ‘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 still needed to elaborate on the therapeutic value of different antihypertensives, especially ARBs and ACE-inhibitors, in daily practice.

As generally acknowledged, it is difficult to generalize efficacy results from clinical trial to ‘real-life’ settings. It is 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 (chapter 4). These differences between clinical trial and the ‘real-life’ setting 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, it is recommendable to combine both efficacy data from clinical trials with effectiveness data from the ‘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 now based on (scarce) evidence from clinical trials. In particular, additional data gathering with 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.

In this thesis, the epidemiological and health-economic aspects of treatment of subjects at increased cardiovascular and renal risk due to elevated albuminuria were studied. In particular, identification and treatment of higher levels of albuminuria was found to be effective in specific populations of patients with type 2 diabetic nephropathy (chapter 1). Here, RAAS intervening agents were found to result in more health gains and cost-savings if applied in an early microalbuminuric stage compared to application in the later stage of overt nephropathy. Therefore, this thesis analysed the opportunities of active screening for albuminuria in the general ‘healthy’ population to intervene in an early disease stage next to treatment of albuminuria in subjects with known diabetes, hypertension, or established cardiovascular or renal disease (chapter 5).

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 are reviewed and discussed in chapter 1 and 5. Existing studies generally base their economic model on the albuminuria-dependent progression to end-stage renal disease in specific patient populations. Next to this, the
economic model could also include data on cardiovascular outcome as was done in our analysis based on the PREVEND-IT study results among generally healthy subjects. Inclusion of cardiovascular outcome in the developed economic model resulted in a favourable cost-effectiveness of population-based screening for and treatment of elevated albuminuria (chapter 6). Furthermore, observational data from the PREVEND study showed that blood-pressure lowering agents are effective in ameliorating cardiovascular outcome. The efficacy of blood-pressure lowering agents (especially RAAS intervening) appeared to be dependent on baseline albuminuria level; the higher baseline albuminuria in hypertensive subjects, the more outspoken the relative risk reduction for cardiovascular disease was (chapter 7). After considering this, 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 elevated levels of albuminuria. Such a population-based screening for albuminuria to prevent both cardiovascular events and renal disease progression in the general population based on clinical trial and observational data, resulted in favourable cost-effectiveness outcomes for different ‘screen-and-treat’ scenarios (chapter 8). Here, the analyses specifically suggest most optimal cost-effectiveness of population-based screening can be achieved if targeted at microalbuminuria in the general population.

In summary, it has been shown in this thesis that treatment with RAAS intervening agents (ARBs and ACE-inhibitors) in subjects at elevated cardiovascular and renal risk is likely to be cost-effective in preventing cardiovascular and/or renal diseases. Early intervention may be more optimal in that respect. 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.

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.