Chapter 8

Cost-Effectiveness of Population-Based ‘Screen-and-Treat’ Strategies for Albuminuria to Prevent Cardiovascular and Renal Disease

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ABSTRACT

Background: Albuminuria has proven to be a renal and cardiovascular risk-marker enabling early diagnosis of subjects at risk. This study aimed to estimate the cost-effectiveness and budget-impact of various population-based ‘screen-and-treat’ scenarios for albuminuria.

Methods: A multi-state transition Markov model was developed to simulate ‘natural course’ albuminuria-based disease progression to dialysis and occurrence of cardiovascular events. Several population-based strategies directed at screening for elevated albuminuria were evaluated. Transition probabilities were derived from the observational community-based PREVEND-cohort study. Health-care costs and life-years gained were calculated over an 8-years period. Given current Dutch discussions, in the base-case analysis screening and treatment for microalbuminuria (urinary albumin concentration ≥20 mg/l and urinary albumin excretion ≥30 mg/day) was analyzed. Other options were investigated in scenario analysis; probabilistic sensitivity analysis was performed.

Results: Assuming 1000 subjects identified with microalbuminuria in the base-case analysis, it was estimated that 76 versus 124 CV-events occur, 16 versus 27 CV-deaths, and 3 versus 5 dialysis cases simulating screening and treatment versus no screening, respectively. The per-person difference in net costs for screening was estimated at €926 (€2,003 versus €1,077) and
prevention of CV-deaths was estimated to gain 0.0421 discounted life years per person. Correspondingly, the cost-effectiveness was estimated at €22,000 per life-year gained. Probabilistic analysis indicated that the probability of a cost-effective ‘screen-and-treat’ strategy was estimated at 54%, 90%, and 95% for a maximum acceptable cost-effectiveness of €20,000, €50,000, and €80,000 per life-year gained, respectively. Higher albuminuria thresholds for screening and treatment further improved the cost-effectiveness, however reduced overall health gains achieved. Also, through limiting screening to those aged over 50 and 60 results became more favourable.

**Conclusion:** Our analyses suggest a potential favourable cost-effectiveness of a population-based screening on albuminuria in the general population. Our results should give health-care decision-makers further tools to consider actual implementation of a population-based screening on albuminuria.

**INTRODUCTION**

End-stage renal disease and cardiovascular (CV) disease are major and growing public-health problems, resulting in increasing financial burdens to society. Early diagnosis and timely start of treatment are essential goals to delay progression to end-stage renal disease and to prevent CV-events.\(^1\,^2\)

Higher levels of albuminuria have proven to be both associated with higher a renal and CV risk. Screening for albuminuria may therefore enable early diagnosis of subjects at risk.\(^3\,^4\) Several studies established that lowering of albuminuria using pharmaceuticals – generally with agents that interfere with the renin-angiotensin-aldosterone system (RAAS) – results in a reduced incidence of CV and renal adverse outcomes in diabetic and hypertensive populations, as well as in the general population.\(^4\,^9\)

Furthermore, there is only limited evidence on cost-effectiveness of screening for microalbuminuria.\(^10\) Given these considerations, it may be worthwhile to implement population-based screening on and treatment of albuminuria in high-risk populations or even the general population in order to prevent CV and renal disease by adequate treatment, possibly already instituted in the early phases of these diseases.\(^1\,^2\,^11\,^12\)

However, before such screening strategies can be implemented several questions should investigated, in particular regarding cost-effectiveness. Firstly, as of yet it is not known which exact albuminuria level to screen for with respect to optimal cost-effectiveness. Secondly, targeting screening to specific age-groups may be more effective than screening the overall population. Obviously, both aspects are crucial in exactly designing a screening program. Thirdly, previous studies that investigated cost-effectiveness of screening for elevated albuminuria were hampered by the
fact that they did not include possible benefits with respect to prevention
of CV disease\textsuperscript{13-15} or only took data into account that were obtained in a
randomized clinical trial.\textsuperscript{10} Inclusion of the full benefits is a prerequisite
for an adequate cost-effectiveness analysis. Furthermore and as generally
acknowledged, randomized clinical trial data may not perfectly reflect
general clinical practice circumstances (e.g. selected populations, fixed
doses). It is therefore important to also take data into account that may
better reflect clinical practice.

The aim of this study was to estimate the cost-effectiveness and
budget-impact of various population-based ‘screen-and-treat’ scenarios
directed at several levels of albuminuria, targeting several age-groups, and
including CV as well as renal outcomes to identify the most favourable
screening strategy. For this purpose, we used data from a prospective
observational study.

\textbf{Methods}

The current analysis was designed for calculating the cost-effectiveness
of a ‘one-off’ screening (one screening, not repeated as a periodical
screening) on albuminuria in the general population. As described below,
a population-based Markov model was developed based on using data
from the observational PREVEND (Prevention of REnal and Vascular
ENdstage Disease) study.\textsuperscript{16} In the model, disease progression and mortality
are quantified by annual transition probabilities, representing the disease
progression or mortality. Supported by actual observational data used (see
below), we assumed that the disease processes can be progressive, as well as
regressive. In particular, the annual transition probabilities and mortality
rates were based on data of the PREVEND study.\textsuperscript{16,17}

\textit{Population}

The PREVEND study is a prospective study designed to investigate the
impact of albuminurï¿½ on the development of renal and CV-events in
the general population. Eligible inhabitants of the city of Groningen, the
Netherlands, were invited to participate (approximately 80,000 persons).
Subjects for detailed study were selected from the 40,856 participating
individuals from this general population. A cohort aged 28-75 years,
enriched for subjects with higher levels of albuminuria, was drawn
from these individuals. A total of 8592 subjects gave written informed
consent and were included in the baseline screening that took place
between 1997 and 1998. These subjects subsequently visited an outpatient
department with approximately 3-year intervals for follow-up screening.
The subsequent screenings allowed actual transitions to be observed and subsequently to be recalcualted on an annual basis (see below). Also, of 8592 subjects included for baseline screening, full pharmacy data were available for 8296 participants through linkage with pharmacy dispensing records of IADB.nl, a database comprising Dutch prescription data.\textsuperscript{18}

In- and exclusion criteria were defined such, to approach the ‘natural course’ of disease progression with respect to albuminuria (figure 1). Pharmacy dispensing records were used to exclude subjects with (previous) use of RAAS-intervening agents. For all subjects included, we excluded the time period after start of all types of antihypertensives for calculating the transition probabilities. Obviously, start of antihypertensives is likely to influence the ‘natural course’ disease progression. Following the Anatomical Therapeutical Chemical (ATC) classification, start of antihypertensives was defined as at least more than one prescription of antihypertensives (ATC = ‘C02’), diuretics (ATC = ‘C03’), β-blockers (ATC = ‘C07’), calcium-channel blockers (ATC = ‘C08’) or RAAS-intervening agents (ATC = ‘C09’) during follow-up.\textsuperscript{19}

\textit{The Model}

A Markov model\textsuperscript{20,21} was used to simulate the natural course of albuminuria progression and regression for the general population in Microsoft Excel 2003. The Markov model consists of eight disease states that reproduce renal disease progression to dialysis and incidence of CV-events (figure 2). In the model, we applied four albuminuria-based states for the progression of renal disease: low-normoalbuminuria (urinary albumin excretion [UAE], 0-15 mg/day), high-normoalbuminuria (UAE, 15-30 mg/day), microalbuminuria (UAE, 30-300 mg/day), and macroalbuminuria (UAE, ≥300 mg/day). The model additionally comprises of four outcome states defined as CV-morbidity, CV-mortality, all-cause mortality (other than CV-mortality), and dialysis.

The model simulates a cohort consisting of 1000 hypothetical subjects from the general population. Subjects can switch between albuminuria states, to the other health states, or remain in the same health state. Here we report on simulations from the Markov model during 8 years, as we felt that this period suffices to render cases with renal and CV-events, whereas the relatively short time horizon (one could also choose a life-time horizon) enhances plausibility, predictive value and validity of the results. Also, an 8-year follow-up coincides with the current duration of the PREVEND-study and data availability for the PREVEND-cohort.
PREVEND Participants (n=8592)

Pharmacy dispensing data available (n=8296)

Population for ‘Natural Course’ disease progression (n=6243)

Inclusion criteria:
Subjects without use of RAAS-intervening treatment in a period of 180 days before baseline screening & during follow-up

Subjects included for calculating annual transition probabilities for the different Markov states for All subjects, those aged >50 and >60.

Low-normo
All : 4956
> 50 : 1554
> 60 : 724

High-normo
All : 676
> 50 : 312
> 60 : 170

Microalb.
All : 557
> 50 : 342
> 60 : 212

Macroalb.
All : 54
> 50 : 32
> 60 : 21

Figure 1  Flow-chart of the inclusion of subjects for calculating the transition probabilities applied in the multi-state Markov model.

Cardiovascular Morbidity

Cardiovascular Mortality

Dialysis

<15 mg/day

15-30 mg/day

30-300 mg/day

≥300 mg/day

Non-Cardiovascular Mortality

Figure 2  Structure of the multi-state Markov model.
Transition Probabilities

Transition probabilities for CV-events and dialysis were calculated following a ‘time-to-first-event’ approach. In particular, we included time until occurrence of the first outcome (CV-morbidity, CV-mortality, dialysis or non-CV mortality) or time until start of antihypertensives or last contact date.

For modelling purposes, the PREVEND-cohort dataset may be conceived as a characteristic one where individuals are monitored through time within irregular measurement intervals that vary over individuals. Furthermore, we note that the information that is collected in the subsequent monitoring visits after baseline screening, reflect the health state of the individual at the moment of visit. The health state at the specific moment of visit does not provide us with information on possible health state changes during the time period between two visits. In other words, during screening visits albuminuria-defined states can be determined, but the exact transition time point between states is unknown. In contrast to this, health outcomes are documented with the exact date on the occurrence of an event, inclusive death. Our multi-state Markov model allows for estimating transition probabilities from data with irregular time intervals between measurements (albuminuria) and health outcomes (CV-disease & dialysis). In particular, transition probabilities for three age-dependent groups (all subjects, age >50, age >60) were estimated using the freely-available R-software \textit{msm} package. The principles of the method for calculating transition probabilities based on a discrete multi-state Markov model in continuous time are described in detail elsewhere. Therefore, here we only present the overall general principles.

In principle, the transition probabilities are estimated based on the \textit{transition intensities}, reflecting the rates of a transition from one health state to the other. Central to the approach is the transition probability matrix, which can be calculated by taking the exponential of the transition intensity matrix. Furthermore, transitions between states are assumed to occur at any time (discrete events in continuous time) within the observed time-intervals and subjects are allowed to progress, regress or remain in the same albuminuria-based state within this time-interval. Health-outcomes states were considered as absorbing states, which did not allow subjects to go through the albuminuria-based model after an event.

Outcome Definitions

Among the observed population, the incidence of CV-morbidity, CV-mortality, dialysis or non-CV-death, was consistently registered during follow-up. The PREVEND database was linked to the database of the national registry of renal replacement therapy (RENNINE) to obtain
information on the status of end-stage renal disease (e.g. dialysis, renal transplantation). Data on hospitalization for CV-morbidity were obtained from PRISMANT, the Dutch national registry of hospital stays. Causes of death were obtained from the Dutch Central Bureau of Statistics. All data were coded according to the International Classification of Diseases (ICD), 9th revision and the classification of interventions. CV-events were defined according to the Major Adverse Cardiovascular Events criteria as acute myocardial infarction (ICD-code 410), acute and subacute ischaemic heart disease (ICD-code 411), subarachnoid haemorrhage (ICD-code 430), intracerebral haemorrhage (ICD-code 431), other intracranial haemorrhage (ICD-code 432), occlusion or stenosis of the precerebral (ICD-code 433) or cerebral arteries (ICD-code 434), coronary artery bypass grafting or percutaneous transluminal angioplasty, and other vascular interventions such as percutaneous transluminal angioplasty or bypass grafting of aorta peripheral vessels.

Screening and Effectiveness

Different population-based screening strategies to identify subjects with elevated albuminuria were defined. In the current approach, screening was assumed to follow the PREVEND-study methodology. In particular, all subjects would be invited to send a vial with first morning void urine by mail to a central laboratory for a pre-screening on urinary albumin concentration (UAC). Those found with elevated levels of albumin in urine would be invited for confirmatory tests, being collection of two 24 hours urines for measurement of 24 hour UAE, with the outcomes being communicated with the general practitioner (GP).

Given current Dutch discussions and the initial design of the PREVEND-study, screening on UAC ≥20 mg/l was investigated in the base-case analysis to pre-select subjects for further UAE measurement and those subjects with confirmed microalbuminuria (UAE ≥30 mg/day) were assumed to receive angiotensin-converting-enzyme (ACE)-inhibitor treatment. In the base-case analysis, this approach was compared with no screening and no treatment for the same modelled cohort. By explicitly using the PREVEND-study data for calculating the number of subjects needed to be screened and tested to finally identify 1000 subjects with confirmed albuminuria, we implicitly accounted for UAC and UAE test characteristics (sensitivity and specificity).

The effectiveness of ACE-inhibitor treatment in preventing CV-events was derived from the randomized clinical Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND IT). The PREVEND IT-study showed that fosinopril resulted in a trend of 40% lower incidence of the primary endpoint of CV-mortality and hospitalization for
CV-morbidity versus no treatment in a population of generally healthy subjects with elevated albuminuria levels. In an observational setting, comparable reductions in CV-events after start of antihypertensive treatment (especially with RAAS-intervening agents) were recently also described for subjects with hypertension and elevated albuminuria levels, reinforcing the above mentioned clinical-trial findings.\(^{28}\) Effectiveness estimates of RAAS-agents on the prevention of end-stage renal disease is not available for the general population and was therefore assumed to be the same as for CV-events. These effectiveness assumptions were varied in univariate and probabilistic sensitivity analyses.

The treatment effect on the progression and regression between the different albuminuria states was derived from the observational PREVEND data.\(^{29}\) Here, the effect of start on RAAS-intervening agents was calculated relative to no such treatment and/or no start of other antihypertensives.

**Costs, Cost-Effectiveness and Budget Impact**

Cost-effectiveness was estimated from the health-care perspective, including medical costs only. Effects in terms of life year gained (LYGs) were estimated based on the extension of life expectancy resulting from intervention within the applied time-horizon of 8 years. Costs of screening and treatment minus savings on CV-events and dialysis was divided by LYGs to render the cost effectiveness ratio (net cost per LYG). Costs and effects of screening were annually discounted according to the Dutch guidelines for pharmacoeconomic research at 4% and 1.5%, respectively, to correct for time preference. All costs were expressed in 2008 Euro’s (€).\(^{30}\)

Costs associated with screening and treatment with RAAS-agents, costs of hospitalization for CV-events and annual dialysis costs are presented in table 1. The costs of screening for albuminuria were based on costs involved with pre-screening on UAC and on confirmatory tests in subjects with elevated UAC (measurement of UAE in two 24 hours urines), including CV and renal risk assessment. In particular, these amounted to be €7 and €60, respectively.\(^{10,31}\) Treatment costs were based on the most frequently used RAAS-intervening agent enalapril.\(^{32,33}\) Further costs related to the prescription fee and to annual GP costs.

The costs of CV-events such as fatal and non fatal myocardial infarction, fatal and non fatal stroke, coronary artery bypass graft surgery, percutaneous transluminal angioplasty and other CV-death and other deaths were adapted from Van Hout *et al* (table 1).\(^{34}\) A weighted average of the CV-costs was calculated using observed data on events derived from the PREVEND-study. The annual costs of current care and dialysis for treatment of end-stage renal disease were based on a study of Van Os *et al* representing a weighted average of active haemodialysis, passive dialysis
and peritoneal dialysis.35 We conservatively only included costs for the first CV-event and did not so for consecutive potential preventable events. To be consistent and again conservative for dialysis, only the costs for one year of treatment were included.

Additionally, a formal incremental cost-effectiveness analysis and an expected budget impact assessment (costs per million population) of different screen-and-treat scenarios were performed, the latter based on overall Dutch population data.14,24

Table 1 Costs included in the model.

<table>
<thead>
<tr>
<th>Events</th>
<th>Cost (€)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-screening on UAC</td>
<td>7</td>
<td>[10]</td>
</tr>
<tr>
<td>Screening on UAE</td>
<td>60</td>
<td>[10,27]</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual treatment with ACE inhibitor</td>
<td>79</td>
<td>[29]</td>
</tr>
<tr>
<td>Annual prescription fee pharmacist</td>
<td>26</td>
<td>[27]</td>
</tr>
<tr>
<td>Annual GP costs</td>
<td>73</td>
<td>[10,27]</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non fatal cardiovascular events†</td>
<td>7,047</td>
<td>[27,30]</td>
</tr>
<tr>
<td>Cardiovascular mortality‡</td>
<td>1,593</td>
<td>[27,30]</td>
</tr>
<tr>
<td>Dialysis (annual costs)</td>
<td>72,460</td>
<td>[27,31]</td>
</tr>
</tbody>
</table>

†Weighted costs based on occurrence of (hospitalisation for) non fatal myocardial infarction, ischaemic heart disease, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, subarachnoidal haemorrhage, intracerebral haemorrhage, other unspecified intracranial haemorrhage, occlusion and stenosis of precerebral arteries, carotis desobstruction, aorta peripheral bypass surgery, percutaneous transluminal femoral angioplasty.
‡Weighted costs based on occurrence of (hospitalisation for) fatal myocardial infarction, fatal ischaemic heart disease, occlusion of cerebral arteries followed by death.

**Scenario Analysis, Deterministic and Probabilistic Sensitivity Analysis**

Scenario analysis was directed at the performance of various ‘screen-and-treat’ strategies based on various threshold values for UAC and UAE levels in different subgroups based on age (all ages, age >50, and age >60 years).

Sensitivity analysis was directed at investigating different time-horizons (5, 8, 10 and 15 years). Further sensitivity analyses were carried out for several relevant input variables. First, a univariate (deterministic) sensitivity analysis was conducted for the various costs estimates (e.g. UAC pre-screening, UAE confirmation test, treatment, event costs) and estimates concerning the effect of pharmacotherapeutic intervention on disease progression and occurrence of events.

Furthermore, we conducted a probabilistic sensitivity analysis to account for uncertainty in multiple relevant parameters included in the
model. A Monte Carlo simulation (10,000 replicates) was used to derive 95% confidence intervals for cost-effectiveness and threshold probabilities. In our model, we included the uncertainty around the effect on the transition probabilities between all albuminuria-based states (regression and progression after start of RAAS-intervening agents) and on the CV and renal outcomes by drawing from the assumed underlying distributions (see Appendix, Table A). In particular, for the uncertainty around the transition probabilities for 'natural course' disease progression, we simulated 10,000 transition probability matrices based on the assumption of asymptotic normality of the maximum likelihood estimates of the log transition intensities. The costs of CV-morbidity and CV-mortality were also drawn from distributions fitted to the observed events and related estimated costs from the PREVEND-cohort study.

**Results**

**Base-case Cost-Effectiveness Analysis**

Figure 2 shows the structure of the multi-state Markov model on which our analyses are based. These transition probabilities were calculated based on a mean follow-up of the PREVEND-cohort of 6.81 ± 1.67 years. The exact annual transition probabilities are given in the Appendix (Table B).

For the base-case, it was estimated that with pre-screening on UAC ≥20 mg/l and ACE-inhibitor treatment of those subjects with confirmed microalbuminuria (UAE ≥ 30 mg/day), a reduced number of CV and renal events occurred if compared with no screening. Based on 8 years of simulation and assuming 1000 subjects identified with microalbuminuria, it was estimated that 76 versus 124 CV-events occur, 16 versus 27 CV-deaths, and 3 versus 5 dialysis cases in the analysis assuming screening and treatment versus no screening, respectively. Net costs for identification of 1 subject with microalbuminuria were calculated at €305. Total discounted per-person net costs following both the screen-and-treat and no-screening strategy are estimated at €2,003 versus €1,077, respectively (difference of €926). Next to this, prevention of CV-mortality is estimated to gain 0.0421 discounted life year per-person identified and treated. Consequently, cost-effectiveness of screening for microalbuminuria with subsequent treatment of those found positive, was estimated to be €22,000 per LYG.

**Scenario-Analyses**

Table 2 shows the cost-effectiveness results for different ‘screen-and-treat’ scenarios based on variation of thresholds for UAC at pre-screening to indicate further evaluation using UAE and on variation of thresholds
for UAE confirmation tests resulting in treatment initiation. This table shows data for the overall population, as well as for subgroups aged >50 and >60 years. Limiting screening to subgroups aged over 50 and 60 years improves cost-effectiveness considerably with cost-effectiveness ratios of respectively €11,500 and €7,800 per LYG, for the initial set of UAC and UAE levels (≥20 mg/l and ≥30 mg/day, respectively). It can be seen that the choice for a UAC pre-screening threshold in combination with the UAE confirmation test for treatment has important influence on the cost-effectiveness. In particular, pre-screening on UAC ≥20 mg/l or ≥100 mg/l in combination with UAE confirmation tests for treatment of UAE ≥30 mg/d or ≥300 mg/l seems to result in most favourable cost-effectiveness.

Sensitivity Analysis

The impact of the different assumptions in the model was assessed in a univariate sensitivity analyses for the initial (base-case) analysis with pre-screening on UAC ≥20 mg/l and treatment confirmation test on UAE ≥30mg/day. These results indicate that a 50% increase or decrease of the costs of CV-morbidity, CV-mortality and dialysis in the base-case analysis with a cost-effectiveness ratio of €22,000 per LYG, results in cost-effectiveness ratios of €17,000 and €26,900 per LYG, respectively. The cost-effectiveness outcome appeared to be most sensitive to the CV-morbidity cost estimate and hardly sensitive to the costs associated with dialysis due to the low number of progressions to dialysis within our time frame of 8 years. Lowering or increasing the costs of pre-screening on UAC, costs for the UAE confirmation test and costs of ACE-inhibitor treatment with 50%, resulted in cost-effectiveness ratios different from the base-case cost-effectiveness of €22,000 per LYG at €19,800 or 24,200; €20,600 or 23,400; and €16,500 or 27,500 per LYG, respectively.

Table 2  Cost-effectiveness ratio’s for different screening scenario’s based on UAC and UAE thresholds and age.

<table>
<thead>
<tr>
<th>UAC threshold for pre-screening</th>
<th>All subjects</th>
<th>Age &gt; 50</th>
<th>Age &gt; 60</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>±15 mg/d</td>
<td>≥30 mg/d</td>
<td>≥300 mg/d</td>
</tr>
<tr>
<td>No</td>
<td>€59,600</td>
<td>€44,200</td>
<td>€112,700</td>
</tr>
<tr>
<td>≥10 mg/l</td>
<td>€40,700</td>
<td>€27,300</td>
<td>€39,600</td>
</tr>
<tr>
<td>≥20 mg/l</td>
<td>€27,800</td>
<td>€22,000</td>
<td>€20,400</td>
</tr>
<tr>
<td>≥100 mg/l</td>
<td>€17,400</td>
<td>€16,500</td>
<td>€14,600</td>
</tr>
<tr>
<td>≥200 mg/l</td>
<td>€20,500</td>
<td>€20,200</td>
<td>€19,900</td>
</tr>
</tbody>
</table>

All cost-effectiveness ratio’s are presented in €’s per Life Year Gained
Applying 0% and 4% discount rates for both costs and effects resulted in changes of the cost-effectiveness ratios in the range €21,400-25,200 per LYG. Results obtained after varying the effectiveness of ACE-inhibitor treatment initiated after screening were as follows: (i) a 25% change in the applied risk reduction (Relative Risk (RR): 0.51 or 0.71, instead of the 0.60 as assumed in the base-case) resulted in cost-effectiveness ranging between €15,700-32,200 per LYG; (ii) a 50% change in the applied risk reduction (RR: 0.41 or 0.80, instead of the 0.60 as assumed in the base-case scenario) resulted in cost-effectiveness ranging between €11,400-51,800. Changing of the effect of the intervention on the progression through albuminuria levels resulted in only slight differences from the base-case cost-effectiveness.

Applying extended time-horizons for the analysis instead of the 8 years assumed in the base-case scenario, resulted in more favourable cost-effectiveness outcomes with €16,900 and €10,800 per LYG for 10 and 15 years, respectively. These changes in cost-effectiveness outcomes are obviously due to the higher numbers of LYGs counted within these extended time-horizons (see figure 3).

**Figure 3** Number of Life Years Gained (LYGs) per 1000 subjects identified and treated with RAAS-intervening agents.
Cost-effectiveness acceptability curves for a screen-and-treat intervention directed at microalbuminuria compared with no screening. *Dotted line*: screening of all subject (base-case) with pre-screening on UAC ≥20 mg/l and confirmation test for treatment on UAE ≥30 mg/day; *Dashed line*: screening procedure as in base-case, but only among subjects aged >50 years; and *Solid line*: screening procedure as in base-case, but only among subjects aged > 60 years.

Additionally, results from the probabilistic sensitivity analysis indicated probabilities that cost-effectiveness would be below various thresholds for maximum willingness-to-pay for one LYG. In the base-case and for maximum willingness-to-pay of €20,000, €50,000 and €80,000 per LYG, the probabilities for accepting the screen-and-treat procedure was estimated at 54%, 90%, and 95%, respectively (figure 4). In subgroups of subjects aged >50 or >60 years, these probabilities were even higher with >80%, >95%, and >97%, respectively (figure 4).

**Incremental Analysis and Budget Impact Analysis**

For the incremental analysis, all possible “screen-and-treat” scenarios for all subjects as given in table 2 were plotted on the cost-effectiveness plane (figure 5). Here, the most favourable scenario with lowest costs and positive effect was identified (A in figure 5). Furthermore, the efficiency frontier was derived after excluding subsequent scenarios with higher incremental costs and lower incremental effects (dominance) and those scenarios that were subject to higher costs and higher incremental cost-effectiveness (extended dominance). For all subjects, the resulting formal efficiency frontier is composed by options for screening on macroalbuminuria.
(A and B in figure 5); by screening options for microalbuminuria (C, E and G in figure 5); and by screening options for UAE ≥15 mg/l (H and I in figure 5). In particular, the base-case analysis with screening on microalbuminuria was on the efficiency frontier. After exclusion of scenarios that were subject to strict dominance, two scenarios with low thresholds for screening on albuminuria remained to be subject to extended dominance (D and F in figure 5).

**Figure 5** Cost-effectiveness plane: the efficiency frontier representing different incremental cost-effectiveness outcomes for screening all subjects presenting the following “screen-and-treat” scenarios (A) UAC ≥200 mg/l & UAE ≥300 mg/day; (B) UAC ≥100 mg/l & UAE ≥300 mg/day; (C) UAC ≥100 mg/l & UAE ≥30 mg/day; (E) UAC ≥20 mg/l & UAE ≥30 mg/day (base-case); (G) UAC ≥10 mg/l & UAE ≥30 mg/day; (H) UAC ≥10 mg/l & UAE ≥15 mg/day; and (I) UAE ≥15 mg/day without UAC pre-screening. The **White** dots represent the scenarios that were subject to strict dominance (excluded for further consideration). The **Grey** dots represent the scenarios that were subject to extended dominance, with “screen-and-treat” scenarios (D) UAC ≥100 mg/l & UAE ≥15 mg/day; and (F) UAC ≥20 mg/l & UAE ≥15 mg/day. The **dashed** lines indicate the cost-effectiveness ratios of €20,000, 50,000, and 80,000 per life-year gained.
The shape of the figure and the incremental cost-effectiveness results were essentially similar for subgroups aged >50 and >60 years, but the efficiency frontier is more favourable when screening would be conducted in subjects at higher age. Also, comparing dots I and H shows that pre-screening of subjects on morning urine sample UAC greatly reduces costs, without losing considerable effect. Though limiting screening and subsequent treatment to only subjects with macroalbuminuria (A and B in figure 5) instead of subjects with microalbuminuria (E and G) may modestly lower the costs, it greatly reduces the effects: the lines for the incremental cost-effectiveness analysis (A,B,C to E) are close to the willingness-to-pay threshold of €20,000 per LYG.

Finally, the budget impact was estimated, using the assumptions in the base-case scenario (UAC ≥20 mg/l and UAE ≥30 mg/day). Budget impact was estimated at €50.2 million per million subjects screened (figure 6). Pre-screening and screening contributed for respectively 13.9% and 8.8% to the total costs. The remaining budget was attributable to costs for GP-visits (31.6%) and costs for treatment (45.7%). Budget impact increased for scenarios directed at those aged above 50 (€68.8 million per million subjects screened) or 60 (€80.6 million per million subjects screened) with relative lower screening costs and relative higher treatment costs due to the higher rate of subjects identified with albuminuria in elderly.
In this study, we estimated the cost-effectiveness of a population-based screening on albuminuria to prevent renal disease progression and CV-events in the general population. Screening consisted of a two-stage approach. First, subjects send by post a vial containing a sample of a first morning urine void in which urinary albumin concentration. Second, in case urinary albumin concentration (UAC) is above a certain cut-off, subjects are invited to collect 24-hours urines for determination of urinary albumin excretion (UAE). The cost-effectiveness of our base-case approach, being a two-stage screening of the general population for microalbuminuria (UAC ≥20 mg/l and UAE ≥30 mg/day) followed by ACE-inhibitor treatment in those found positive, was estimated at €22,000 per LYG. Limiting screening to only those aged >50 or >60 years resulted in a more favourable cost-effectiveness ratio. Also, we found considerable probabilities that the base-case ‘screen-and-treat’ procedure would be considered cost-effective by varying the ‘willingness-to-pay’ thresholds (€20,000/LYG, €50,000/LYG, €80,000/LYG) according to reasonable and applied country-specific thresholds.

Although we found favourable cost-effectiveness results for restricted screening in those subjects at higher age and/or higher albuminuria levels, screening in selected populations coincides with lower absolute numbers of subjects identified for potential successful preventive treatment. In other words, implementation of screening on, for example macroalbuminuria results in smaller absolute numbers of subjects that are likely to be identified and smaller numbers of events prevented. Thus, scenarios of screening directed at macroalbuminuria or within higher age-groups, potentially decrease the likelihood that subjects at elevated risk for CV and renal disease are identified and treated in an early phase.

Using strict health-economic terminology, the initial base-case analysis for screening on microalbuminuria was on the efficiency frontier, excluding (extended) dominated alternatives. These dominated and excluded strategies involve higher costs and/or (relatively) lower effects of screening for elevated albuminuria. This is important, although we do note here that it has previously been argued that in general dominated strategies should not automatically be excluded for further decision-making or consideration, although rigorous application of health-economic decision rules might suggest so. Yet, similar consistent patterns for all subjects and subgroups on age indicate that the current alternatives on the efficiency frontier are most likely to represent the most favourable strategies. In particular, 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 choice.
How do the current study results compare to what is known in literature? Only two studies have attempted as yet to estimate the cost-effectiveness of population-based screening and treatment for albuminuria. Boulware et al. investigated cost-effectiveness of initial dipstick screening for proteinuria in the general population, with follow-up proteinuria confirmation tests to differentiate on starting ACE-inhibitor treatment. These authors reported higher cost-effectiveness rates than ours, varying from US $53,400 to $282,800 per quality adjusted life-year gained. In particular, these higher cost-effectiveness rates were due to the method of screening (using dipsticks that are only positive in case of proteinuria (macroalbuminuria; UAC ≥20 mg/l), which resulted in fewer subjects identified compared to screening for albuminuria by nephelometry, as in our study, which can also measure low amounts of urinary albumin loss (microalbuminuria; UAC ≥20 mg/l). Consequently, in such an approach there will be higher costs to identify one subject to be found positive. Most importantly, Boulware et al. took only those savings and health gains into account that were related to averted deaths and end-stage renal disease, whereas we focused on the savings with RAAS-interfering agents in the prevention of both CV as well as renal disease. If in our study scenario is chosen to screen only for higher levels of albuminuria (proteinuria) and only savings and health gains for end-stage renal disease are included, it corroborates the findings of Boulware et al. insofar that no favourable cost-effectiveness for early identification and treatment of proteinuria for the general population would exist. Only one other study reported on this issue. It suggested, based on results from a small-scale randomized clinical trial, favourable cost-effectiveness for screening the general population on elevated albuminuria in the general population to prevent albuminuria associated outcomes with ACE-inhibitor treatment. Our current study adds to these two studies that if observational data on both CV-events and renal disease events are considered, population-based screening on microalbuminuria with subsequent ACE-inhibitor treatment results in a favourable cost-effectiveness.

Obviously, our study has limitations. Inherent to the fact that we used for our study a time-horizon of 8 years, dialysis, being a rare complication as a first event, was not found in large numbers. This could also partially be explained by a competing risk for CV-events. This means that subjects are generally at higher initial risk for a CV-event as compared to the risk of renal disease events (e.g. dialysis) which takes more time to occur. Also, our current approach assumes a one-off screening without repeated screening (for example, annual). Future cost-effectiveness studies should analyse the influence of applying intervals for repeated screening. Finally, although varied in the sensitivity analysis, the applied time-horizon of
8 years was not life-time, as is often recommended for health-economic analyses. Yet, one could argue that the cost-effectiveness of a ‘screen-and-treat’ strategy directed at microalbuminuria would have favoured from an extended life-time time-horizon (for example, inclusion of more LYGs through preventing a CV-death in younger subjects) and inclusion of all relevant subsequent events over the full span of life-time. This means that our results are expected to be a conservative estimate.

Strengths of our study are that we used population-based observational data, next to efficacy data from clinical trials. Use of such heterogeneous (general) population data, rather than data from a controlled setting, gives the opportunity to evaluate the real-life ‘natural-course’ albuminuria-related renal disease progression and occurrence of CV and renal events. The population data that are used concern furthermore, a large cohort of community dwelling participants, with extensive information on risk-factors, medication use and various outcome measures. These data were collected prospectively and based on objective data from independent databases, thereby minimising selection and/or recall bias. Lastly, albuminuria was measured quantitatively with nephelometry and confirmed in consecutive 24-hours urine collections, which is considered the gold standard for assessing albuminuria. It also enables to investigate the cost-effectiveness for various cut-off values of albuminuria.

Several studies have shown that microalbuminuria is associated with worse CV and renal disease prognosis. Our favourable cost-effectiveness results for screening on microalbuminuria, together with further potentials to improve the cost-effectiveness are promising. In particular, pre-screening on UAC turns out to be an efficient tool to decrease the costs of population-based screening for elevated albuminuria. Altogether, these results should lead to increased awareness of the importance of albuminuria-measurements in clinical practice and offer decision-makers tools to seriously consider the potentials of population-based screening directed at albuminuria.

The current analyses were conducted from a health-care perspective and not from a societal perspective. In further research, it could be considered to assess further effects of screening on quality-adjusted expectancy of life and including non-medical costs within the societal perspective. Also, it may be considered to also include additional gains in terms of (early) identification of other diseases as it has been shown that microalbuminuria may not only follow, but also precede the development of diabetes and of hypertension. Finally, cost-effectiveness of repeated screening should be calculated based on relevant screening intervals to exactly identify the most favourable and acceptable options.
CONCLUSIONS

In conclusion, our analyses suggest a potential favourable and most optimal cost-effectiveness of a population-based screening on microalbuminuria in the general population as compared to other alternatives, such as screening for macroalbuminuria. Our results are based on previously published randomized clinical trial and observational findings on the effectiveness and efficacy of antihypertensives in the prevention of CV and renal events in specific populations and in the general populations. Based on the current assumptions, our results are likely to be representative for real-life settings. Therefore, it is worthwhile for health-care decision-makers to consider practical implementation of population-based screening on and treatment of albuminuria.

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REFERENCES


42. Vandenbroucke JP. Benefits and harms of drug treatments. Observational studies and randomized trials should learn from each other. BMJ 2004;329:2-3.
### Table A  Annual transition probabilities in the model

<table>
<thead>
<tr>
<th>Annual transition probabilities ('Natural Course')</th>
<th>All subjects</th>
<th>Age &gt;50 yrs</th>
<th>Age &gt;60 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-normoalbuminuria to high-normoalbuminuria (λ1):</td>
<td>0.016</td>
<td>0.021</td>
<td>0.021</td>
</tr>
<tr>
<td>Low-normoalbuminuria to microalbuminuria (λ2):</td>
<td>0.0029</td>
<td>0.0036</td>
<td>0.0050</td>
</tr>
<tr>
<td>Low-normoalbuminuria to macroalbuminuria (λ3):</td>
<td>6.33*10⁻⁵</td>
<td>1.40*10⁻⁵</td>
<td>2.93*10⁻⁵</td>
</tr>
<tr>
<td>High-normoalbuminuria to microalbuminuria (λ4):</td>
<td>0.040</td>
<td>0.046</td>
<td>0.055</td>
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<td>High-normoalbuminuria to macroalbuminuria (λ5):</td>
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<td>0.00019</td>
<td>0.00034</td>
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<td>High-normoalbuminuria to low-normoalbuminuria (λ6):</td>
<td>0.073</td>
<td>0.054</td>
<td>0.038</td>
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<tr>
<td>Microalbuminuria to macroalbuminuria (λ7):</td>
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<td>0.0074</td>
<td>0.011</td>
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<tr>
<td>Microalbuminuria to high-normoalbuminuria (λ8):</td>
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<td>0.018</td>
<td>0.018</td>
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<tr>
<td>Microalbuminuria to low-normoalbuminuria (λ9):</td>
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<td>Macroalbuminuria to microalbuminuria (λ10):</td>
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<td>0.032</td>
<td>0.033</td>
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<td>Macroalbuminuria to high-normoalbuminuria (λ11):</td>
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<tr>
<td>Non-cardiovascular mortality</td>
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<tr>
<td>Low-normoalbuminuria (λ13):</td>
<td>0.0028</td>
<td>0.0071</td>
<td>0.013</td>
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<tr>
<td>High-normoalbuminuria (λ14):</td>
<td>0.0055</td>
<td>0.0086</td>
<td>0.013</td>
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<tr>
<td>Microalbuminuria (λ15):</td>
<td>0.014</td>
<td>0.022</td>
<td>0.026</td>
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<tr>
<td>Macroalbuminuria (λ16):</td>
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<td>0.047</td>
<td>0.075</td>
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<tr>
<td>Cardiovascular morbidity</td>
<td></td>
<td></td>
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<tr>
<td>Low-normoalbuminuria (λ17):</td>
<td>0.0038</td>
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<td>High-normoalbuminuria (λ18):</td>
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<tr>
<td>Microalbuminuria (λ19):</td>
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<td>Macroalbuminuria (λ20):</td>
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<td>Cardiovascular mortality</td>
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<tr>
<td>High-normoalbuminuria (λ22):</td>
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<tr>
<td>Microalbuminuria (λ23):</td>
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<td>0.0049</td>
<td>0.0071</td>
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<td>Macroalbuminuria (λ24):</td>
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<td>Dialysis</td>
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<td>2.96*10⁻⁷</td>
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<td>High-normo (λ26):</td>
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<tr>
<td>Microalbuminuria (λ27):</td>
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<td>Macroalbuminuria (λ28):</td>
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### Table B  Distributions and parameters on input-variables

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<th>Input variables</th>
<th>Distribution</th>
<th>RR (mean)</th>
<th>Standard Deviation</th>
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<tr>
<td><strong>Effect on transition probabilities</strong></td>
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<td>15-30 to &lt;15</td>
<td>Log-normal</td>
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<td>15-30 to 30-300</td>
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<td>30-300 to &lt;15</td>
<td>Log-normal</td>
<td>1.41</td>
<td>1.16</td>
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<td>30-300 to &lt;15-30</td>
<td>Log-normal</td>
<td>1.16</td>
<td>1.18</td>
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<tr>
<td>30-300 to ≥300</td>
<td>Log-normal</td>
<td>0.76</td>
<td>1.51</td>
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<td>≥300 to 30-300</td>
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<td>1.45</td>
<td>1.50</td>
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<td><strong>Effect on health outcomes</strong></td>
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<tr>
<td>CV-morbidity</td>
<td>Log-normal</td>
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<td>CV-mortality</td>
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<td>1.35</td>
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<td>Dialysis</td>
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<td><strong>Cost parameters</strong></td>
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