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Screen-and-Treat Strategies for Albuminuria to Prevent Cardiovascular and Renal Disease: Cost-Effectiveness of Nationwide and Targeted Interventions Based on Analysis of Cohort Data From the Netherlands

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ABSTRACT

Background: Albuminuria is a marker for renal and cardiovascular (CV) risk, allowing early diagnosis of subjects with elevated renal and CV risk.

Objective: This study aimed to estimate the cost-effectiveness and budget impact of various population-based screen-and-treat scenarios for elevated albuminuria levels (ie, microalbuminuria) in the Netherlands.

Methods: A multistate transition Markov model was developed to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of CV events. Several population-based strategies directed at screening for elevated albuminuria were evaluated. These strategies depended on urinary albumin concentration (UAC), urinary albumin excretion (UAE), and age. Transition probabilities were derived from the observational community-based Prevention of Renal and Vascular End Stage Disease (PREVEND) cohort study. Health care costs (in year-2008 euros) and life-years gained were calculated over an 8-year period. In the base-case analysis, we analyzed screening for and treatment of microalbuminuria. Screening for microalbuminuria involved prescreening for UAC ≥ 20 mg/L, followed by a confirmation test for UAE ≥ 30 mg/d. Other options based on combinations of albuminuria for UAC prescreening (no prescreening, and ≥ 10 , ≥ 20 , ≥ 100 , and ≥ 200 mg/L) and UAE confirmation test (≥ 15 , ≥ 30 , and ≥ 300 mg/d) for treatment were investigated in scenario analyses. Furthermore, these various strategies based on UAC and UAE values were analyzed in different subgroups based on age (all ages, aged ≥ 50 years, and aged ≥ 60 years).

Results: The PREVEND study included 8592 Dutch residents aged 28 to 75 years at the time of initial screening. Among a hypothetical cohort of 1000 subjects identified and treated in the base-case analysis, it was estimated (based on PREVEND follow-up data) that, in the screening/treatment and no-screening scenarios, 76 versus 124 CV events occurred, 16 versus 27 CV deaths, and 3 versus 5 dialysis cases, respectively. The per-person difference in net costs for screening was calculated at €926 (€2003 vs €1077), and prevention of CV deaths was estimated to gain 0.0421 discounted life-year per person. Correspondingly, the cost-effectiveness was estimated at €22,000 per life-year gained. In the base-case analysis, probabilistic sensitivity analysis indicated that the likelihood of cost-effectiveness of a screen-and-treat strategy was 54%, 90%, and 95% for a maximum acceptable cost-effectiveness threshold of €20,000, €50,000, and €80,000 per life-year gained, respectively. Higher albuminuria thresholds for screening and start of treatment further improved the cost-effectiveness but reduced the overall health gains achieved. Limiting screening to those subjects aged ≥ 50 and ≥ 60 years resulted in more favorable cost-effectiveness compared with population-based screening without age restriction.

Conclusions: Our analyses suggest the potentially favorable cost-effectiveness of population-based screen-

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ing for albuminuria in the general Dutch population. The results offer health care decision-makers new tools for considering actual implementation of such screening. (*Clin Ther.* 2010;32:1103–1121) © 2010 Excerpta Medica Inc.

Key words: cost-effectiveness, screening, microalbuminuria, cardiovascular disease, renal disease.

INTRODUCTION

End-stage renal disease and cardiovascular (CV) disease are major and growing public health problems, resulting in increasing financial burdens to society.^{1,2} Early diagnosis and timely start of treatment are essential goals to delay progression to end-stage renal disease and to prevent CV events.^{3,4}

Urinary albumin excretion (UAE) values between 0 and 15 mg/d are generally considered to be normal. Overall, albuminuria >15 mg/d (particularly microalbuminuria [UAE ≥30 mg/d] and macroalbuminuria [UAE ≥30 mg/d]) has been reported to be both associated with significantly higher renal and CV risk.^{5,6} Several studies established that reducing albuminuria using pharmaceuticals—typically with agents that interfere with the renin–angiotensin–aldosterone system (RAAS)—is associated with a reduced incidence of CV and renal adverse outcomes in diabetic and hypertensive populations, as well as in the general population.^{6–12} Previously, screening for elevated albuminuria was recommended as routine measurement among those in primary practice with CV and renal risk.⁶ Therefore, it may be worthwhile to implement population-based screening for and early treatment of albuminuria in high-risk populations (eg, hypertension, diabetes) or the general population to prevent CV and renal disease by adequate treatment.^{3,4,13,14} Such active screening targeted at specific subgroups or even screening of the general population would require efficient selection strategies and adequate testing methods.^{3,4,15} Various screening approaches have been advocated or applied, such as screening by means of a dipstick albuminuria self-test at home or by sending a urine sample to a central laboratory.³ After a positive test result, individuals are advised to visit their primary care provider for a confirmation test and additional routine renal and CV-risk profiling, which potentially result in treatment.

However, before such screening strategies can be implemented, several issues should be explored. First, it is not yet known what threshold for elevated albu-

minuria (ie, microalbuminuria or macroalbuminuria) would be most likely to result in an optimal cost-effectiveness (ie, most effective scenario for relative low costs) for screening the general Dutch population. Second, targeting screening to specific age groups may be more cost-effective than screening the overall population. Obviously, both aspects are crucial in designing a screening program. There is only limited evidence regarding the cost-effectiveness of screening for elevated albuminuria; existing studies for the general population were further hampered by the fact that they considered the possible benefits of prevention of renal disease alone, and not CV disease.^{16–18} Furthermore, economic analyses can be limited if only data from randomized clinical trials are included.¹²

The aim of this study was therefore 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 favorable screening strategy. For this purpose, we used data from a prospective, observational study.

METHODS

The current analysis was designed to calculate the cost-effectiveness of a nationwide one-off screening (ie, one screening, not repeated as a periodic screening) for albuminuria in the general Dutch population. A Markov model was developed using data from the observational Prevention of Renal and Vascular End Stage Disease (PREVEND) study.^{19,20} In the model, disease progression and mortality were quantified by annual transition probabilities, representing the disease progression or mortality. Supported by actual observational data used, we assumed that the disease processes can be progressive, as well as regressive. The annual transition probabilities and mortality rates were based on data from the PREVEND study.

Population

The PREVEND study was a prospective study designed to investigate the impact of albuminuria on the development of renal and CV events in the general population. Details of this study have been published elsewhere.^{21,22} Eligible inhabitants of the city of Groningen, the Netherlands, were invited to participate (~80,000 persons). Subjects for detailed study were selected from the 40,856 participating individuals from this general population. A cohort aged 28 to 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. The prevalence of microalbuminuria and the prevalence of chronic kidney disease were found to be comparable in different country-specific settings.^{3,19,23} These subjects subsequently visited an outpatient department with ~3-year intervals for follow-up screening. The subsequent screenings allowed actual transitions to be observed and subsequently to be recalculated on an annual basis. Also, among the 8592 subjects included for baseline screening, full pharmacy data were available for 8296 participants through linkage with the pharmacy dispensing records of IADB.nl, a database comprising Dutch prescription data.²⁴ All subjects included in the PREVEND study gave informed consent to link with pharmacy-dispensing data.

Inclusion and exclusion criteria were defined 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, we excluded the time period after initiation of any type of antihypertensive to calculate the transition probabilities. Obviously, initiation of antihypertensives was likely to influence the natural course of disease progression. Following the anatomical–therapeutic–chemical (ATC) classification, initiation of antihypertensives was defined as ≥ 1 prescription for an antihypertensive (ATC code C02), diuretic (ATC code C03), β -blocker (ATC code C07), calcium-channel blocker (ATC code C08), or RAAS-intervening agents (ATC code C09) during follow-up.²⁵

Model Design

A Markov model was used to simulate the natural course of albuminuria progression and regression for the general population in Windows Excel 2003 (Microsoft Corporation, Redmond, Washington).^{26,27} The current Markov model consisted of 8 disease states that reproduced renal disease progression to dialysis and incidence of CV events (Figure 2). In the model, we applied 4 albuminuria-based states for the progression of renal disease: low normoalbuminuria (UAE < 15 mg/d), high normoalbuminuria (UAE 15–30 mg/d), microalbuminuria (UAE 30–300 mg/d), and macroalbuminuria (UAE ≥ 300 mg/d).⁶ The model additionally comprised 4 outcome states defined as CV morbidity, CV mortality, all-cause mortality (other than CV mortality), and di-

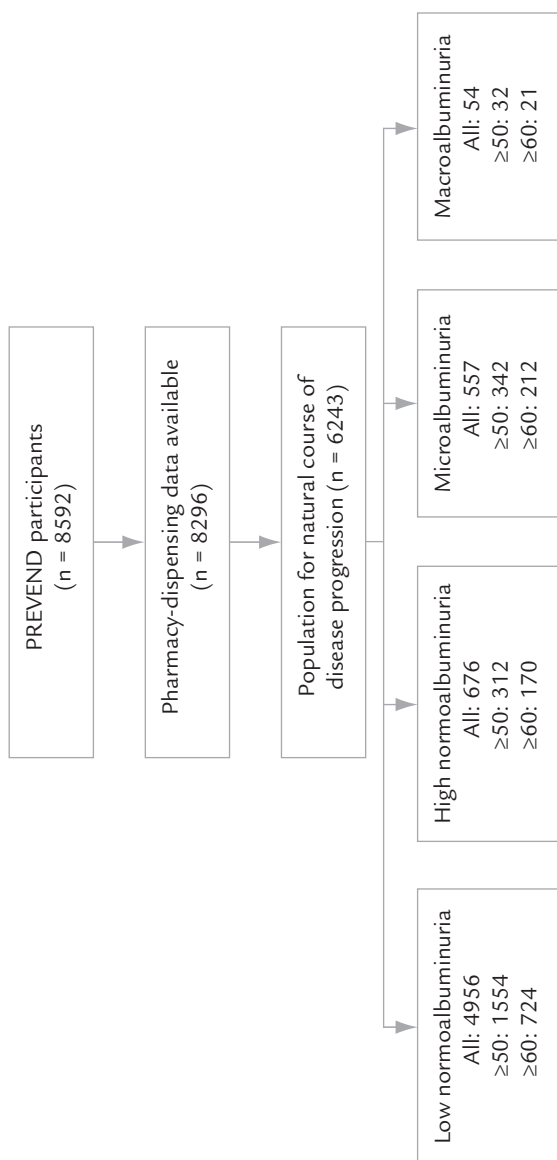
alysis. Long-term costs and effects of an albuminuria-based screen-and-treat intervention relied on estimations of the initial distribution of a patient cohort over albuminuria-based model states and assumptions about how patients move between these health states. These movements—known as transition probabilities—are affected by the intervention of interest potentially resulting in different health outcomes.

The model used in this analysis simulated a cohort of 1000 hypothetical subjects with elevated albuminuria that were identified based on screening the general population. Subjects could switch between albuminuria states, to the other health states, or remain in the same health state. In our base-case analysis, we performed simulations in the Markov model for 8 years, which we considered a sufficient time for renal and CV events to occur in the selected population, whereas the relatively short time horizon (vs a lifetime horizon) enhanced plausibility, predictive value, and validity of the results. Also, an 8-year follow-up coincided with the duration of the PREVEND study and data availability for the PREVEND cohort.

Transition Probabilities

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

For modeling purposes, the PREVEND cohort data could be considered a characteristic one in which individuals were monitored through time within irregular measurement intervals that varied over individuals. Furthermore, the information that was collected in the subsequent monitoring visits after baseline screening reflected the health state of the individual *at the moment* of the visit. The health state at the specific moment of the visit did not provide information regarding possible health-state changes during the time period between visits. In other words, during screening visits, albuminuria-defined states could be determined, but the exact transition time point between states was unknown. In contrast, health outcomes were documented with the exact date of an event, including death. Therefore, we chose to use a multistate Markov approach that included all available prospective data (eg, albuminuria measurements, health outcomes) of individuals included for the PREVEND study.²⁸ This approach offered the opportunity



Study cohort:
 First screening, 1997–1998
 Aged 28–75 years
 Enriched for higher albuminuria levels

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

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

Figure 1. Flow chart of the inclusion of subjects for calculating the transition probabilities applied in a multistate Markov model to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events in the Netherlands. PREVIEW = Prevention of Renal and Vascular End Stage Disease cohort study; RAAS = renin-angiotensin-aldosterone system; low normoalbuminuria = urinary albumin excretion (UAE) 0–15 mg/d; high normoalbuminuria = UAE 15–30 mg/d; microalbuminuria = UAE 30–300 mg/d; macroalbuminuria = UAE ≥300 mg/d.

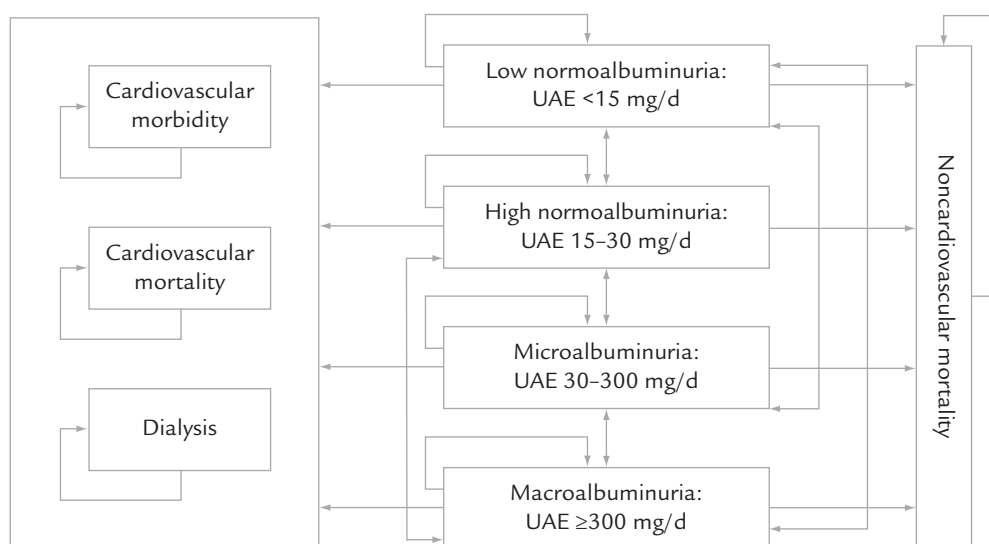


Figure 2. Structure of a multistate Markov model to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events in the Netherlands. UAE = urinary albumin excretion.

to account for changes in albuminuria levels (eg, assuming a certain pattern) between 2 measurements. Therefore, our multistate Markov model allowed for estimating transition probabilities from data with irregular time intervals between measurements (albuminuria) and health outcomes (CV disease and dialysis).^{28,29} In particular, transition probabilities for 3 age-dependent groups (all subjects, aged ≥ 50 years, aged ≥ 60 years) were estimated using the freely available R software *MSM* package.³⁰ The principles of the method for calculating transition probabilities based on a discrete multistate Markov model in continuous time have been described in detail elsewhere.²⁸⁻³⁰ Therefore, we only present the overall principles.

The transition probabilities are, in principle, estimated based on the *transition intensities* derived from the original data, reflecting the rates of a transition from one health state to another. Central to this approach was calculating a transition probability matrix that included all possible transition probabilities. The transition probability matrix could be calculated by taking the exponent of the transition intensity matrix. Furthermore, transitions between states were assumed to occur at any time (discrete events in continuous time) within the observed time intervals and subjects were allowed

to progress, regress, or remain in the same albuminuria-based state within this time interval. Health-outcomes states were considered absorbing states, which did not allow subjects to go through the albuminuria-based model after an event.

Outcome Definitions

Among the observed population, the incidences of CV morbidity, CV mortality, dialysis, or non-CV death were registered during follow-up. The PREVENT database was linked to the database of the national registry of renal replacement therapy to obtain information about the status of end-stage renal disease (eg, dialysis, renal transplantation).³¹ Data on hospitalization for CV morbidity were obtained from the Dutch national registry of hospital stays.³² Causes of death were obtained from the Dutch Central Bureau of Statistics.³³ All data were coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)* and the classification of interventions. CV events were defined according to the major adverse CV events criteria as acute myocardial infarction (*ICD-9* code 410), acute and subacute ischemic heart disease (*ICD-9* code 411), subarachnoid hemorrhage (*ICD-9* code 430), intracerebral hemorrhage (*ICD-9* code 431), other intracranial

hemorrhage (*ICD-9* code 432), occlusion or stenosis of the precerebral (*ICD-9* code 433) or cerebral arteries (*ICD-9* 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 prescreening of urinary albumin concentration (UAC). Only those identified with elevated levels of albumin in urine would be invited for confirmatory tests, beginning with collection of two 24-hour urine samples for measurement of 24-hour UAE. This confirmation test for UAE, which is considered an accepted standard method for the measurement of albuminuria,⁶ was assumed to be conducted in the primary care level.⁴

The ability of a test to identify individuals of interest relies on the test characteristics (eg, sensitivity, specificity), but it is also greatly dependent on the setting in which the test is conducted (eg, self-test at home vs laboratory test).^{3,4} In particular, the home setting could be considered less than ideal for reliable testing when compared with a laboratory. Therefore, for the current analysis, it was assumed that individuals first sent their urine vials to a central laboratory for prescreening for albuminuria; those who tested positive were assumed to have been invited for a confirmation test in the primary care setting.

Given current Dutch discussions and the initial design of the PREVEND study,^{3,20} prescreening for UAC ≥ 20 mg/L was investigated in the base-case analysis to preselect subjects for further UAE measurement, and those subjects with confirmed microalbuminuria (UAE ≥ 30 mg/d) were assumed to receive angiotensin-converting enzyme inhibitor (ACEI) treatment. In the base-case analysis, this approach was compared with no screening and no treatment for the same modeled cohort. By explicitly using the PREVEND study data to calculate the number of subjects needed to be screened and tested to finally identify and treat 1000 subjects with confirmed albuminuria, we implicitly accounted for UAC and UAE test characteristics (sensitivity and specificity).

The effectiveness of ACEI treatment in preventing CV events was derived from the randomized clinical PREVEND Intervention Trial (PREVEND IT).¹⁰ PREVEND IT showed that fosinopril was associated with a 40% lower incidence of the primary end point of CV mortality and hospitalization for CV morbidity versus no treatment in a population of generally healthy subjects with albuminuria. In an observational setting, comparable reductions in CV events after initiation of antihypertensive treatment (especially with RAAS-intervening agents) were recently described for subjects with hypertension and elevated albuminuria levels, reinforcing the previously mentioned clinical trial findings.³⁴ It was assumed in the model that subjects with elevated albuminuria were not yet treated or not treated well, based on the findings of the previously mentioned studies among heterogeneous populations with or without background therapies.^{10,34} Effectiveness estimates of RAAS agents on the prevention of end-stage renal disease were not available for the general population and were 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, following the method previously described by Brantsma et al.³⁵ Brantsma et al found a net regression in albuminuria for the general Dutch population. For the purpose of the current study, a comparable analysis was conducted to evaluate the effect of initiating RAAS-intervening agents on the progression or regression in UAE relative to no such treatment and/or no start of other antihypertensives. These relative differences in disease progression were applied to our Markov model to reflect the effect of screening with targeted intervention versus no screening on the transition probabilities between albuminuria-based health states.

Costs, Cost-Effectiveness, and Budget Impact

Cost-effectiveness was estimated from the health care perspective, including medical costs only. Effects in terms of life-years 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 were divided by the number of LYGs to render the cost-effectiveness ratio (ie, 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 year-2008 euros.³⁶

Costs associated with screening and treatment with RAAS agents, costs of hospitalization for CV events, and annual dialysis costs are presented in **Table I**. The costs of screening for albuminuria were based on costs involved with prescreening on UAC and on confirmatory tests in subjects with elevated UAC (measurement of UAE in two 24-hour urine samples), including CV and renal risk assessment. In particular, these amounted to €7 for prescreening and €60 for the confirmation test (including 2 primary care visits and two 24-hour UAE measurements) among those found UAC positive following the prescreening, respectively.^{12,37} Treatment costs were based on the most frequently used RAAS-intervening agent, enalapril.^{38,39} Further costs were related to the prescription fee and to annual primary care costs.

The costs of CV events such as fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, coronary artery bypass graft surgery, percutaneous transluminal angioplasty, and other CV deaths, and other deaths were adapted from van Hout and Simoons⁴⁰ (**Table I**). A weighted mean of the CV costs was calculated using observed data regarding events derived from PREVEND. 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,⁴¹ representing a weighted mean of active hemodialysis, passive dialysis, and peritoneal dialysis. We conservatively included only costs for the first CV event and did not include subsequent, potentially preventable events. To be consistent and conservative for dialysis, only the costs for 1 year of treatment were included.

Additionally, a formal incremental cost-effectiveness analysis and an expected budget impact assessment (costs per 1 million people) of different screen-and-treat scenarios were performed, the latter based on overall Dutch population data.^{17,30}

Scenario Analysis, Deterministic Sensitivity Analysis, 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, aged ≥ 50 years, and aged ≥ 60 years).

Table I. Costs included in a multistate Markov model to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events in the Netherlands.

Event	Cost, Year-2008, €
Screening	
Prescreening of UAC ¹²	7
Screening of UAE ^{12,37}	60
Treatment	
Annual treatment with ACE inhibitor ³⁸	79
Annual prescription fee pharmacist ³⁷	26
Annual primary care costs ^{12,37}	73
Outcomes	
Nonfatal cardiovascular events ^{37,40*}	7047
Cardiovascular mortality ^{37,40†}	1593
Dialysis ^{37,41‡}	72,460

UAC = urinary albumin concentration; UAE = urinary albumin excretion; ACE = angiotensin-converting enzyme.

*Weighted costs based on occurrence of hospitalization for nonfatal myocardial infarction, ischemic heart disease, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, subarachnoid hemorrhage, intracerebral hemorrhage, other unspecified intracranial hemorrhage, occlusion and stenosis of precerebral arteries, carotid desobstruction, aorta peripheral bypass surgery, or percutaneous transluminal femoral angioplasty.

†Weighted costs based on occurrence of hospitalization for fatal myocardial infarction, fatal ischemic heart disease, or occlusion of cerebral arteries followed by death.

‡Only the annual costs for the first year of dialysis were included in the model.

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 (ie, deterministic) sensitivity analysis was conducted for the various cost estimates (eg, UAC prescreening, 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% CI values for cost-effectiveness and threshold probabilities.^{42,43} In our model, we included the uncertainty around the effect on the transition probabilities between all albuminuria-based states (regression and progression after initiation of RAAS-intervening agents) and on the CV and renal outcomes by drawing from the assumed underlying distributions (Appendix I).^{10,20} In particular, for the uncertainty around the transition probabilities for the natural course of 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.³⁰ 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.²⁰

RESULTS

Base-Case Cost-Effectiveness Analysis

Figure 2 shows the structure of the multistate Markov model on which our analyses were based. The PREVEND study included 8592 Dutch residents aged 28 to 75 years at the time of the initial screening. The transition probabilities used in the present analysis were calculated using the mean (SD) follow-up time from the PREVEND cohort of 6.81 (1.67) years. The exact annual transition probabilities are given in Appendix II.

For the base-case scenario, it was estimated that with prescreening on UAC ≥ 20 mg/L and ACEI treatment of those subjects with confirmed microalbuminuria (UAE ≥ 30 mg/d), 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 would occur, 16 versus 27 CV deaths, and 3 versus 5 dialysis cases in the analysis assuming screening and treatment versus no screening, respectively. Total costs for screening 10,000 subjects from the general Dutch population were estimated to amount to €114,000 (including €70,000 for UAC prescreening and €44,000 for UAE confirmation test among those subjects found UAC positive) for the identification of 373 subjects with microalbuminuria (UAE ≥ 30 mg/d). Therefore, net costs for identification of 1 subject with microalbuminuria based on screening the general Dutch population were calculated at €305. Total discounted per-person net costs following both the screen-and-treat and no-screening strategy were estimated at €2003

versus €1077, respectively (difference of €926). Prevention of CV mortality was estimated to gain 0.0421 discounted life-year per person identified and treated. Consequently, screening for microalbuminuria with subsequent treatment of those identified as positive was found to be cost-effective, estimated at €22,000/LYG.

Scenario Analyses

Table II shows the cost-effectiveness results for different screen-and-treat scenarios based on variation of thresholds for UAC at prescreening 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 ≥ 50 and ≥ 60 years improved cost-effectiveness considerably with cost-effectiveness ratios of respectively €11,500 and €7800 per LYG, for the initial set of UAC and UAE levels (≥ 20 mg/L and ≥ 30 mg/d, respectively). The choice for a UAC prescreening threshold in combination with the UAE confirmation test for treatment influenced the cost-effectiveness. In particular, in combination with UAE confirmation tests for treatment of UAE ≥ 300 mg/d, prescreening for UAC ≥ 20 or ≥ 100 mg/L seemed to result in the most favorable cost-effectiveness outcomes, producing values of €20,400 and €14,600/LYG, respectively (Table II).

Sensitivity Analyses

The impact of the different assumptions in the model was assessed in a univariate sensitivity analyses for the initial (base-case) analysis with prescreening for UAC ≥ 20 mg/L and treatment confirmation test for UAE ≥ 30 mg/d. These results indicated 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/LYG resulted in cost-effectiveness ratios of €17,000 and €26,900/LYG, respectively. The cost-effectiveness outcome appeared to be most sensitive to the CV morbidity cost estimate and relatively insensitive to the costs associated with dialysis because of the low number of incidents of progression to dialysis within our time frame of 8 years. Lowering or increasing the costs of prescreening on UAC, costs for the UAE confirmation test, and costs of ACEI treatment by 50% resulted in cost-effectiveness ratios different from the base-case cost-effectiveness of €22,000/LYG with €19,800/LYG or €24,200/LYG for varying costs

Table II. Cost-effectiveness ratios for different screening scenarios based on age and thresholds for urinary albumin concentration (UAC) and urinary albumin excretion in a multistate Markov model to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events in the Netherlands. All values are shown as year-2008 euros per life-year gained.

UAC Threshold for Prescreening	All Subjects			Aged ≥ 50 Years			Aged ≥ 60 Years		
	≥ 15 mg/d	≥ 30 mg/d	≥ 300 mg/d	≥ 15 mg/d	≥ 30 mg/d	≥ 300 mg/d	≥ 15 mg/d	≥ 30 mg/d	≥ 300 mg/d
No prescreening	59,600	44,200	112,700	25,100	20,800	47,600	14,100	13,400	48,300
≥ 10 mg/L	40,700	27,300	39,600	17,800	13,500	18,000	10,500	8900	18,900
≥ 20 mg/L	27,800	22,000	20,400	13,500	11,500	11,200	8600	7800	11,700
≥ 100 mg/L	17,400	16,500	14,600	9100	8900	8100	7500	7500	7900
≥ 200 mg/L	20,500	20,200	19,900	10,700	10,600	10,500	9600	9600	10,100

of UAC prescreening; €20,600/LYG or €23,400/LYG for varying costs of the UAE confirmation test; and €16,500/LYG or €27,500/LYG for varying ACEI costs, respectively. Applying 0% and 4% discount rates to both costs and effects resulted in changes of the cost-effectiveness ratios in the range €21,400 to €25,200/LYG. Results obtained after varying the effectiveness of ACEI treatment initiated after screening were as follows: (1) a 25% change in the applied risk reduction (relative risk [RR] = 0.51 or 0.71, instead of 0.60 as assumed in the base-case scenario) resulted in cost-effectiveness ranging from €15,700 to €32,200/LYG; and (2) 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 from €11,400 to €51,800. Changing of the effect of the intervention on the progression through albuminuria levels with $\pm 50\%$ resulted in only slight differences (€22,000 \pm €200/LYG) 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 favorable cost-effectiveness outcomes

of €16,900 and €10,800/LYG for 10 and 15 years, respectively. These changes in cost-effectiveness outcomes may have been the result of the higher numbers of LYGs noted for these extended time horizons (Figure 3).

Additionally, results from the probabilistic sensitivity analysis indicated probabilities that cost-effectiveness would be below various thresholds for maximum willingness to pay for 1 LYG. In the base-case analysis and for maximum willingness to pay of €20,000, €50,000, and €80,000/LYG, the probabilities for accepting the screen-and-treat procedure were estimated at 54%, 90%, and 95%, respectively (Figure 4). In age subgroups, these probabilities were even higher at 80%, 95%, and 97% for ≥ 50 years, and 88%, 97%, and 98% for ≥ 60 years (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 II were plotted on the cost-effectiveness plane (Figure 5). Here, the most favorable scenario with lowest costs and positive effect was identified (point A in Figure 5). Further-

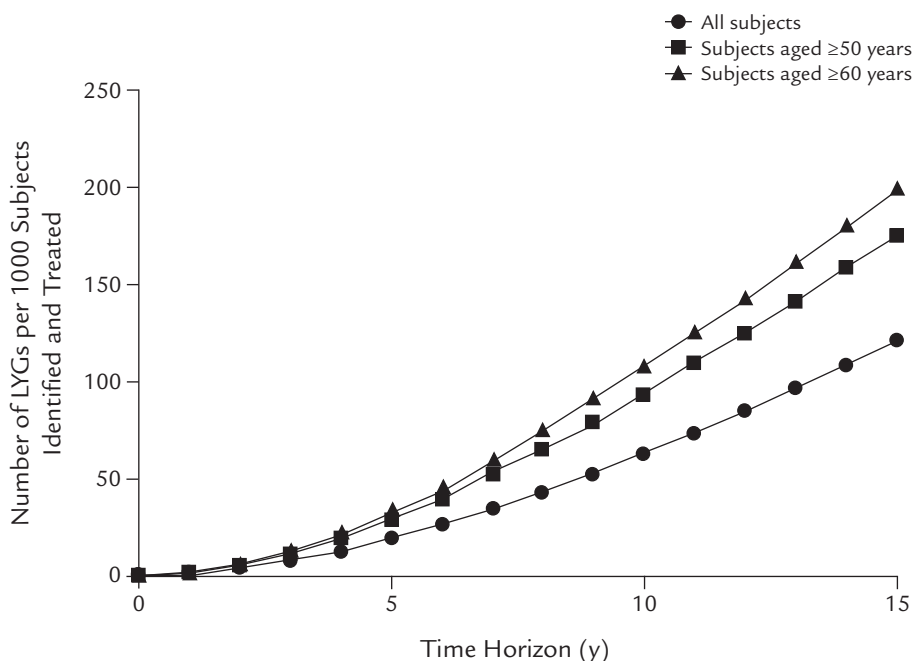


Figure 3. Number of life-years gained (LYGs) per 1000 subjects identified and treated with renin-angiotensin-aldosterone system-intervening agents in a multistate Markov model to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events in the Netherlands.

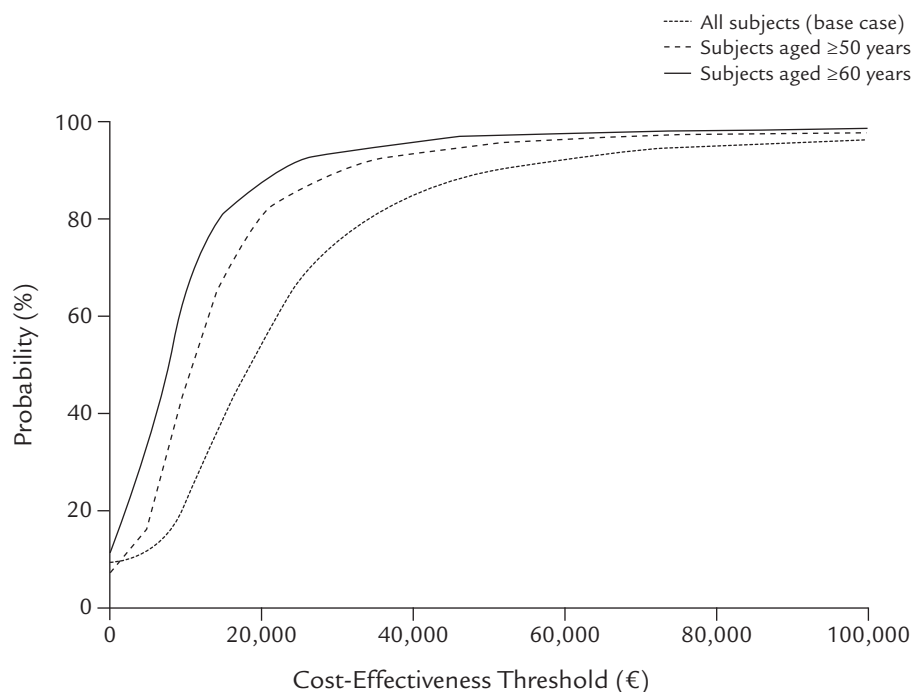


Figure 4. Cost-effectiveness acceptability curves for screen-and-treat intervention directed at microalbuminuria compared with no screening in a multistate Markov model to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events in the Netherlands.

more, 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).⁴⁴ For all subjects, the resulting formal efficiency frontier is composed by options for screening on macroalbuminuria (points A and B in Figure 5); by screening options for microalbuminuria (points C, E, and G in Figure 5); and by screening options for UAE ≥ 15 mg/L (points H and I in Figure 5). In particular, the base-case analysis with screening for microalbuminuria was on the frontier of efficiency. After exclusion of 6 scenarios that were subject to strict dominance (no prescreening and UAE ≥ 30 mg/d; no prescreening and UAE ≥ 300 mg/d; UAC ≥ 10 mg/L and UAE ≥ 300 mg/d; UAC ≥ 20 mg/L and UAE ≥ 300 mg/d; UAC ≥ 200 mg/L and UAE ≥ 15 mg/d; and UAC ≥ 200 mg/L and UAE ≥ 30 mg/d), 2 scenarios with low thresholds for screening for albuminuria remained to be subject to extended dominance.

Figure 5 shows that scenario E (UAC ≥ 100 mg/L and UAE ≥ 15 mg/d) was dominated by a combination of scenarios C and E. Scenario F (UAC ≥ 20 mg/L and UAE ≥ 15 mg/d) was similarly dominated by a combination of scenarios E and G. The shape of Figure 5 and the incremental cost-effectiveness results were essentially similar for subgroups aged ≥ 50 and ≥ 60 years, but the efficiency frontier was more favorable when screening would be conducted in older subjects. Also, comparing points H and I shows that prescreening subjects using the UAC of morning urine samples would greatly reduce costs without losing considerable effect. Although limiting screening and subsequent treatment to only those subjects with macroalbuminuria (points A and B in Figure 5) instead of subjects with microalbuminuria (points E and G) would modestly lower costs, it would also greatly reduce the effect: the slope of the lines for the incremental cost-effectiveness analysis (A to B, B to C, C to E) are close to the willingness-to-pay threshold of €20,000/LYG.

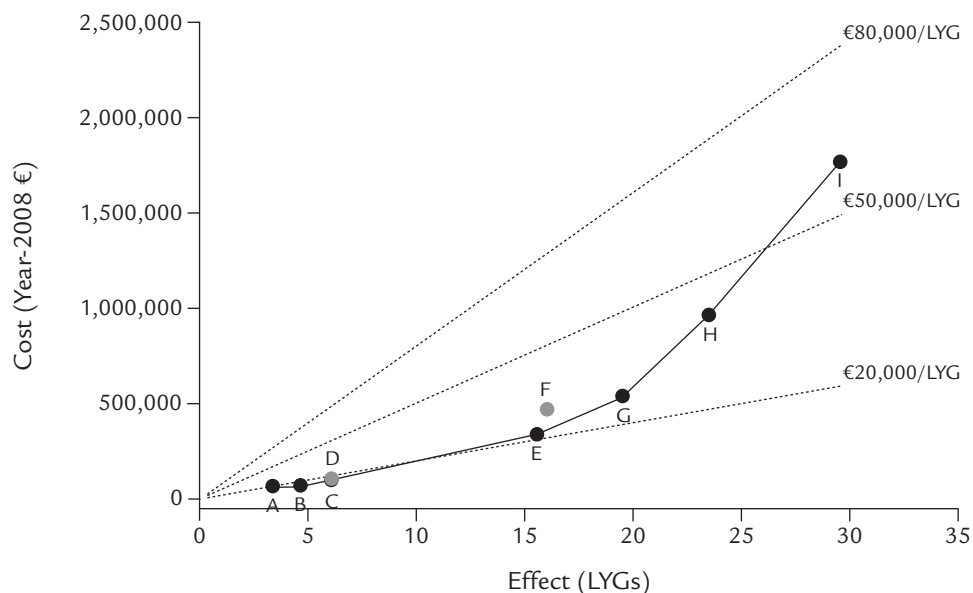


Figure 5. Incremental cost-effectiveness ratios for screening among all subjects presenting specified screen-and-treat scenarios in a multistate Markov model to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events in the Netherlands. Costs and effects were based on screening 10,000 of the population of all subjects. (A) Urinary albumin concentration (UAC) ≥ 200 mg/L and urinary albumin excretion (UAE) ≥ 300 mg/d. (B) UAC ≥ 100 mg/L and UAE ≥ 300 mg/d. (C) UAC ≥ 100 mg/L and UAE ≥ 30 mg/d. (D) Extended dominance: UAC ≥ 100 mg/L and UAE ≥ 15 mg/d. (E) UAC ≥ 20 mg/L and UAE ≥ 30 mg/d (base case). (F) Extended dominance: UAC ≥ 20 mg/L and UAE ≥ 15 mg/d. (G) UAC ≥ 10 mg/L and UAE ≥ 30 mg/d. (H) UAC ≥ 10 mg/L and UAE ≥ 15 mg/d. (I) UAE ≥ 15 mg/d without UAC prescreening. LYG = life-year gained.

Finally, the budget impact was estimated, based on a one-off screening without including incident subjects with elevated albuminuria using the assumptions in the base-case scenario (UAC ≥ 20 mg/L and UAE ≥ 30 mg/d). Budget impact was estimated at €50.2 million per million subjects screened over an 8-year period (Figure 6). Furthermore, the budget impact estimated over a 1- and 5-year period after screening was respectively calculated at €17.6 million and €38.3 million per million subjects screened. Prescreening and screening contributed 13.9% and 8.8% to the total costs, respectively. The remaining budget was attributable to costs for primary care visits, including cost for albuminuria tests and routine blood pressure measurements (31.6%) and costs for treatment (45.7%). The proportion of total costs attributable to screening for the first year after screening were ~2 to 3 times higher than screening costs over 5 or 8 years, with 64%, 30%, and 23% noted for years 1, 5, and 8,

respectively. Budget impact increased for scenarios directed at those aged ≥ 50 years (€68.8 million per million subjects screened) or ≥ 60 years (€80.6 million per million subjects screened) with relatively lower screening costs and relative higher treatment costs because of the higher rate of subjects identified with albuminuria in the older population.

DISCUSSION

In this study, we estimated the cost-effectiveness of population-based screening for albuminuria to prevent renal disease progression and CV events in the general population based on data derived from the PREVENT study. Screening consisted of a 2-stage approach. First, subjects provided (by postal delivery) a vial containing a sample of a first morning urine void for measuring UAC. Second, if UAC exceeded a predetermined cut-off, subjects were invited to collect 24-hour samples to

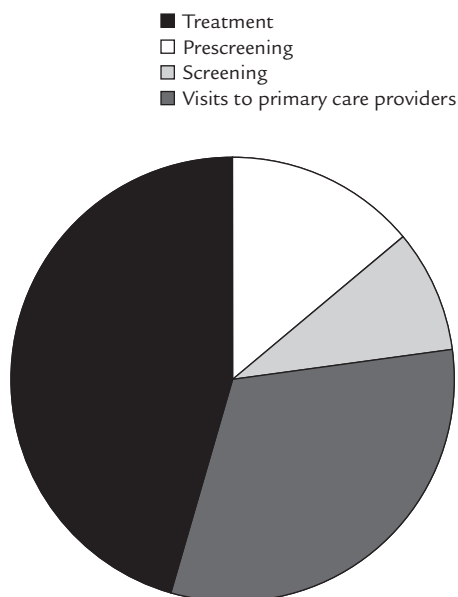


Figure 6. Distribution of the total estimated budget impact of €50.2 million over 8 years per million subjects screened for albuminuria in the base-case analysis (all subjects, prescreening of the first morning urine void for urinary albumin concentration ≥ 20 mg/L and confirmation in two 24-hour urine voids with urinary albumin excretion ≥ 30 mg) in a multi-state Markov model to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events in the Netherlands.

determine UAE. The cost-effectiveness of our base-case approach, being a 2-stage screening of the general population for microalbuminuria (UAC ≥ 20 mg/L and UAE ≥ 30 mg/d) followed by ACEI treatment in those found to test positive, was estimated at €22,000/LYG. Limiting screening to only those aged ≥ 50 or ≥ 60 years resulted in a more favorable cost-effectiveness ratio. Also, we found a great likelihood that the base-case screen-and-treat procedure would be cost-effective according to the different willingness-to-pay thresholds (€20,000, €50,000, and €80,000/LYG) that were applied.

Although we found favorable cost-effectiveness results for restricted screening in those subjects who were older or had higher albuminuria levels, screening in selected populations would coincide with lower absolute numbers of subjects identified for potential successful preventive treatment.¹⁹ Thus, scenarios of screening directed at macroalbuminuria or within older age groups reduce the likelihood that subjects at elevated risk for CV and renal disease would be identified and treated in an early stage of disease development.³

Using strict health-economic terminology, the initial base-case analysis for screening for microalbuminuria was on the efficiency frontier. This efficiency frontier consisted of all strategies that were most likely to be accepted based on their cost-effectiveness outcome. Thus, the extended dominated strategies that involved higher costs and/or relatively lower effects of screening for elevated albuminuria were excluded. These strategies consisted of clinically irrational or irrelevant options for population-based screening. This is important, although we note that it has been previously argued that, in general, dominated strategies should not automatically be excluded for further decision-making or consideration, but rigorous application of health-economic decision rules might suggest this would be the proper course of action.⁴⁵ On the other hand, consistent patterns for all subjects and age subgroups suggest that the current alternatives on the efficiency frontier are most likely to represent the most favorable strategies. In particular, screening for microalbuminuria was associated with relatively high incremental effects for relatively low additional costs and could therefore be considered to potentially reflect the optimal choice.

Only 2 published studies have previously attempted to estimate the cost-effectiveness of population-based screening and treatment for albuminuria.^{12,17} Boulware et al¹⁶ investigated cost-effectiveness of initial dipstick screening for proteinuria in the general population, with follow-up proteinuria confirmation tests to determine the need to initiate ACEI treatment. Boulware et al reported higher cost-effectiveness rates than those noted in the present model analysis, 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 [ie, macroalbuminuria at UAC ≥ 20 mg/L]), which resulted in fewer subjects identified compared with screening for albuminuria by nephelometry, as in PREVEND,²⁰ which can also mea-

sure low amounts of urinary albumin loss (ie, microalbuminuria at UAC ≥ 20 mg/L). Consequently, given such an approach, there would be higher costs to identify one subject who met the predetermined threshold.¹⁶ Moreover, 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 in the prevention of both CV events and renal disease.^{16,17} If, in our study, we had chosen to consider a screen-and-treat scenario directed only at greatly elevated levels of albuminuria (proteinuria) and included savings and health gains for end-stage renal disease without considering CV events, results would have been expected to corroborate the findings of Boulware et al in that such a favorable cost-effectiveness for early identification and treatment of proteinuria for the general population would not have existed.^{4,16} Only one other published study addressed this issue, suggesting (based on results from a small-scale randomized clinical trial) favorable cost-effectiveness for screening the general population for elevated albuminuria to prevent albuminuria-associated outcomes by initiating ACEI treatment in identified subjects.¹² Our analysis adds that if observational data on both CV events and renal disease events are considered, population-based screening for microalbuminuria with subsequent ACEI treatment would yield favorable cost-effectiveness.

Our analysis has limitations. Inherent to the fact that we used a time horizon of 8 years, dialysis (being a rare complication as a first event) was not found in many patients. This could be partially explained by a competing risk for CV events, meaning that subjects would generally be at higher initial risk for a CV event compared with the risk of renal disease events (eg, dialysis) that take more time to develop.⁴⁶ Also, our current approach assumes a one-off screening without repeated screening. Therefore, only those subjects with elevated albuminuria (eg, microalbuminuria) would be included at any given moment of screening without identifying incident cases in the following years. Future cost-effectiveness studies should analyze the influence of applying intervals for repeated screening, which requires inclusion of more specific data on the natural course of disease development (eg, age-specific incidence of microalbuminuria). Finally, although varied in the sensitivity analysis, the applied time horizon of 8 years was not a lifetime horizon (as is often recommended for health-economic analyses). On the other hand, one could argue that the cost-effectiveness of a screen-and-treat strategy directed

at microalbuminuria would have benefited from an extended lifetime time horizon (ie, inclusion of more LYGs through preventing a CV death in younger subjects) and inclusion of all relevant subsequent events over the full span of the lifetime. This means that our results would be expected to be a conservative estimate. At the same time, our results are based on consistent use of treatment and do not account for therapy adherence, but effectiveness results measured among individuals with albuminuria in a real-life setting implicitly include nonadherence³⁴; current cost-effectiveness results could be overestimated by not explicitly accounting for nonadherence.

Inclusion of the full benefits is a prerequisite for adequate cost-effectiveness analysis. Furthermore, randomized clinical trial data may not perfectly reflect general clinical practice circumstances (eg, selected populations, fixed doses). Therefore, it is important to also take data into account that may better reflect clinical practice.

The strengths of our study are that we used population-based observational data, rather than efficacy data from clinical trials. Use of such heterogeneous (ie, general) population data, rather than data from a controlled setting, gives the opportunity to evaluate the real-life natural course of albuminuria-related renal disease progression and occurrence of CV and renal events.⁴⁷ The population data that are used concern a cohort 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 minimizing selection, recall bias, or both. Finally, albuminuria was measured quantitatively with nephelometry and assessed in a first morning urine sample (prescreening) and confirmed in 2 consecutive 24-hour urine collections (actual screening). This is considered an accepted standard approach for assessing albuminuria.^{6,20} It also allows the investigation of the cost-effectiveness of different screening scenarios using various thresholds to define abnormal albuminuria levels.

Several studies have reported that microalbuminuria was associated with significantly worse CV (2-fold increase in UAC associated with a 30% increase in CV mortality) and renal disease prognosis (diminished renal function; $P = 0.001$).^{48,49} Our favorable cost-effectiveness results for screening for microalbuminuria are promising. In particular, prescreening for UAC is an efficient tool for decreasing the costs of population-based screening for elevated albuminuria. Overall, these results

should lead to increased awareness of the importance of albuminuria measurements in clinical practice and offer decision-makers new tools to consider the potential of population-based screening directed at albuminuria.¹⁴ We should also be aware of the limited health care budgets and competition with other valuable preventive health care interventions. However, it seems that the relatively low costs for screening on elevated albuminuria and targeted intervention could lead to considerable reductions in the burden of illness caused by CV and renal disease events over time.

The current analyses were conducted from a health care perspective and not from a societal perspective. Further research should assess the effects of screening on quality-adjusted LYGs and include nonmedical costs from the societal perspective. It should also include additional gains in terms of early identification of other diseases because microalbuminuria may not only follow but also precede the development of diabetes or hypertension.^{50,51} Finally, the cost-effectiveness of repeated screening should be calculated.

CONCLUSIONS

Our analyses suggest the potentially favorable cost-effectiveness of population-based screening for microalbuminuria in the general Dutch population compared with other alternatives, such as screening for macroalbuminuria. Our findings are based on a previously published randomized clinical trial and observational findings about the effectiveness and efficacy of antihypertensives in the prevention of CV and renal events. The results offer health care decision-makers new tools for considering actual implementation of such screening.

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Appendix I. Parameters of input variables in a multistate Markov model to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events in the Netherlands. All variables had a log-normal distribution.

Input Variables	Value
Effect parameters, mean (SD), relative risk	
Effect on transition probabilities	
Transition in urinary albumin excretion	
15-30 to <15 mg/d	1.23 (1.07)
15-30 to 30-300 mg/d	0.74 (1.16)
30-300 to <15 mg/d	1.41 (1.16)
30-300 to <15-30 mg/d	1.16 (1.18)
30-300 to ≥300 mg/d	0.76 (1.51)
≥300 to 30-300 mg/d	1.45 (1.50)
Effect on health outcomes	
Cardiovascular morbidity	0.61 (1.35)
Cardiovascular mortality	0.61 (1.35)
Dialysis	0.61 (1.35)
Cost parameters, mean (SD), year-2008 €	
Cardiovascular morbidity	7047 (3140)
Cardiovascular mortality	1593 (846)

Appendix II. Annual transition probabilities in a multistate Markov model to simulate the natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events in the Netherlands.

Annual Transition Probabilities*	All Subjects	Aged ≥50 Years	Aged ≥60 Years
Low normoalbuminuria to high normoalbuminuria	0.016000000	0.021000000	0.021000000
Low normoalbuminuria to microalbuminuria	0.002900000	0.003600000	0.005000000
Low normoalbuminuria to macroalbuminuria	0.000063300	0.000014000	0.000029300
High normoalbuminuria to microalbuminuria	0.040000000	0.046000000	0.055000000
High normoalbuminuria to macroalbuminuria	0.000640000	0.000190000	0.000340000
High normoalbuminuria to low normoalbuminuria	0.073000000	0.054000000	0.038000000
Microalbuminuria to macroalbuminuria	0.000530000	0.007400000	0.011000000
Microalbuminuria to high normoalbuminuria	0.033000000	0.018000000	0.018000000
Microalbuminuria to low normoalbuminuria	0.021000000	0.015000000	0.010000000
Macroalbuminuria to microalbuminuria	0.030000000	0.032000000	0.033000000
Macroalbuminuria to high normoalbuminuria	0.000530000	0.000320000	0.000330000
Macroalbuminuria to low normoalbuminuria	0.000340000	0.000260000	0.000180000
Noncardiovascular mortality			
Low normoalbuminuria	0.002800000	0.007100000	0.013000000
High normoalbuminuria	0.005500000	0.008600000	0.013000000
Microalbuminuria	0.014000000	0.022000000	0.026000000
Macroalbuminuria	0.023000000	0.047000000	0.075000000
Cardiovascular morbidity			
Low normoalbuminuria	0.003800000	0.008300000	0.012000000
High normoalbuminuria	0.010000000	0.020000000	0.026000000
Microalbuminuria	0.017000000	0.027000000	0.033000000
Macroalbuminuria	0.032000000	0.051000000	0.060000000
Cardiovascular mortality			
Low normoalbuminuria	0.000260000	0.000690000	0.001200000
High normoalbuminuria	0.000570000	0.001700000	0.003500000
Microalbuminuria	0.003200000	0.004900000	0.007100000
Macroalbuminuria	0.011000000	0.018000000	0.015000000
Dialysis†			
High normoalbuminuria	0.000000296	0	0
High normoalbuminuria	0.000003730	0	0
Microalbuminuria	0.000110000	0	0
Macroalbuminuria	0.004700000	0	0

Low normoalbuminuria = urinary albumin excretion (UAE) 0–15 mg/d; high normoalbuminuria = UAE 15–30 mg/d; microalbuminuria = UAE 30–300 mg/d; and macroalbuminuria = UAE ≥300 mg/d.

*Natural course of albuminuria-based disease progression to dialysis and occurrence of cardiovascular events.

†The few number of patients undergoing dialysis resulted in a low probability of transition to dialysis for all subjects or none at all for those aged ≥50 years or ≥60 years.