University of Groningen

Cost-effectiveness of screening for albuminuria with subsequent fosinopril treatment to prevent cardiovascular events

Atthobari, J.; Asselbergs, F.W.; Boersma, C.; de Vries, R.; Hillege, H.L.; van Gilst, W.H.; Gansevoort, R.T.; de Jong, P.E.; de Jong-van den Berg, L.T.W.; Postma, M.J.

Published in:
Clinical Therapeutics

DOI:
[10.1016/j.clinthera.2006.03.012](https://doi.org/10.1016/j.clinthera.2006.03.012)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Atthobari, J., Asselbergs, F. W., Boersma, C., de Vries, R., Hillege, H. L., van Gilst, W. H., Gansevoort, R. T., de Jong, P. E., de Jong-van den Berg, L. T. W., & Postma, M. J. (2006). Cost-effectiveness of screening for albuminuria with subsequent fosinopril treatment to prevent cardiovascular events: A pharmacoeconomic analysis linked to the prevention of RENal and vascular ENDstage disease (PREVEND) study and the prevention of RENal. *Clinical Therapeutics*, 28(3), 432-444.
<https://doi.org/10.1016/j.clinthera.2006.03.012>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Cost-Effectiveness of Screening for Albuminuria with Subsequent Fosinopril Treatment to Prevent Cardiovascular Events: A Pharmacoeconomic Analysis Linked to the Prevention of RENal and Vascular ENdstage Disease (PREVEND) Study and the Prevention of RENal and Vascular ENdstage Disease Intervention Trial (PREVEND IT)*

Jarir Atthobari, MD¹; Folkert W. Asselbergs, MD²; Cornelis Boersma, MSc¹; Robin de Vries, MSc¹; Hans L. Hillege, PhD³; Wiek H. van Gilst, PhD²; Ron T. Gansevoort, PhD⁴; Paul E. de Jong, PhD⁴; Lolkje T.W. de Jong-van den Berg, PhD¹; and Maarten J. Postma, PhD¹; for the PREVEND IT Study Group

¹Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen University Institute for Drug Exploration, Groningen, The Netherlands; ²Department of Clinical Pharmacology, Groningen University Institute for Drug Exploration, Groningen, The Netherlands; ³Trial Coordination Center, Groningen University Institute for Drug Exploration, Groningen, The Netherlands; and ⁴Department of Internal Medicine, Department of Nephrology, Groningen University Institute for Drug Exploration, Groningen, The Netherlands

ABSTRACT

Objective: This study estimated the cost-effectiveness, from the Dutch health care perspective, of screening for albuminuria in the general Dutch population to prevent cardiovascular events (CVEs) with subsequent angiotensin-converting enzyme inhibitor treatment, using data from the Prevention of RENal and Vascular ENdstage Disease Intervention Trial (PREVEND IT).

Methods: PREVEND IT was a single-center, double-blind, randomized, placebo-controlled trial with a 2 × 2 factorial design within the larger observational Prevention of RENal and Vascular ENdstage Disease (PREVEND) study. The PREVEND IT study was conducted to assess the effects of fosinopril 20 mg and pravastatin 40 mg on CVEs in subjects with specific inclusion criteria: urinary albumin excretion (UAE) rate in the range from 15 to 300 mg/d, blood pressure <160/100 mm Hg, and plasma cholesterol level <8.0 mmol/L. Cost-effectiveness estimates for the Dutch population were expressed in euros (2002; 1€ = US \$1.01) as net costs per life-year gained (LYG) in the baseline and sensitivity (stochastic) analyses.

Results: Data were assessed for 864 subjects, with a mean (SD) follow-up of 46 (7) months. CVEs occurred in 45 (5.2%) subjects. Subjects who received

fosinopril had a 40% lower incidence of CVEs than subjects in the placebo group (3.9% vs 6.5%, respectively; *P* = NS). The cost-effectiveness of screening for albuminuria was determined to be €16,700/LYG for the study population. Stochastic analysis indicated that the probability of the cost-effectiveness being below the suggested Dutch threshold of €20,000/LYG was 59% in the baseline analysis. The probability of cost-effectiveness below €20,000/LYG would increase to 91% if only subjects with UAE >50 mg/d were treated with fosinopril. Limiting the screening to subjects aged >50 years and >60 years also improved cost-effectiveness.

Conclusions: The results of our study suggest that screening the general Dutch population for albuminuria and subsequently treating those found positive with fosinopril may be cost-effective compared with no screening and adopting the Dutch health care per-

*The Dutch PREVEND IT investigators are listed in the Acknowledgments.

Accepted for publication January 31, 2006.

doi:10.1016/j.clinthera.2006.03.012

0149-2918/06/\$19.00

Printed in the USA. Reproduction in whole or part is not permitted. Copyright © 2006 Excerpta Medica, Inc.

spective. However, confirmation from larger multicenter trials is needed. (*Clin Ther.* 2006;28:432–444) Copyright © 2006 Excerpta Medica, Inc.

Key words: cost-effectiveness analysis, fosinopril, urinary albumin excretion, cardiovascular disease.

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death in many countries.^{1,2} In The Netherlands, CVD accounts for ~11% of all health care costs.³ Microalbuminuria, defined as a slightly elevated albumin level (urinary albumin excretion [UAE] >30 and <300 mg/d), is a marker associated with an increased risk for cardiovascular (CV) morbidity and mortality in subjects with diabetes^{4,5} or hypertension,⁶ and in the general population.^{7–9} Screening for microalbuminuria, either alone or in combination with screening for hypertension and hypercholesterolemia, may be a useful tool to identify subjects at risk for CVD and/or progressive renal failure.¹⁰ Use of antihypertensive agents has been shown to be effective in reducing the incidence of cardiovascular events (CVEs).¹¹ Antihypertensive interventions, particularly with angiotensin-converting enzyme (ACE) inhibitors, have been reported to lower UAE in subjects with or without diabetes, and in those with essential hypertension.^{11,12} However, it is not known whether an intervention focusing specifically on the reduction of UAE will result in a decrease in CVEs. Therefore, the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)¹³ was designed to assess the effects of an ACE inhibitor on the incidence of CVEs in subjects with elevated UAE.

Various trials have reported the benefits of CVD prevention. In studies reporting the cost-effectiveness of secondary prevention,^{14–18} most have found favorable cost-effectiveness for the use of ACE inhibitors in preventing CVEs in high-risk subjects. However, there have been few investigations of their cost-effectiveness in primary prevention, particularly with respect to nephrology markers.^{19,20} Prevention based on albuminuria measurement in the general community may be an option for primary prevention. Golan et al²¹ reported that treatment with ACE inhibitors in subjects with macroalbuminuria (UAE >300 mg/d) and diabetic nephropathy was cost-effective in preventing end-stage renal disease. Palmer et al²² found that the use of angiotensin-receptor antagonists in subjects with dia-

betes was more cost-effective, when compared with other antihypertensives used to improve life expectancy, if treatment was started during the early microalbuminuria stage (ie, UAE >30 mg/d). However, Boulware et al²³ found that screening the general population for albuminuria was not cost-effective when considering renal outcomes (end-stage renal disease). As of the time of writing, no cost-effectiveness study has been directed at the prevention of CVEs (PubMed; up to 2005; key terms: *cost-effectiveness, albuminuria, cardiovascular disease*). Therefore, the present study aimed to investigate the cost-effectiveness of screening for albuminuria to prevent CVEs with ACE-inhibitor treatment using data from the Prevention of Renal and Vascular Endstage Disease (PREVEND) and PREVEND IT.^{8,13,24,25}

PREVEND IT compared the effect of the ACE inhibitor fosinopril and the 3-hydroxy-3-methylglutaryl-coenzyme A-reductase inhibitor pravastatin on the incidence of CVEs in subjects with albuminuria (>15 mg/d) and normal blood pressure and serum cholesterol levels.¹³ During a 4-year treatment period, fosinopril was associated with a significant reduction in albuminuria compared with placebo (20.9% decrease vs 4.7% increase, respectively; $P < 0.001$) and numerically fewer CVEs ($P = \text{NS}$). The fosinopril group had a 40% lower incidence of CVEs compared with the placebo group (number needed to treat [NNT], 38). Subjects with microalbuminuria (>50 mg/d) had a 60% lower incidence of CVEs than those in the placebo group (NNT, 13). Pravastatin treatment was not associated with a significant reduction in albuminuria or a significant change in the incidence of CVEs (4.8% decrease related to pravastatin vs 5.6% in placebo; hazard ratio, 0.87 [95% CI, 0.49–1.57]). Because the present analysis was based on the nonsignificant trend toward fewer CVEs with fosinopril in PREVEND IT, it should be interpreted as a hypothesis-generating study whose findings need confirmation in larger multicenter trials.

SUBJECTS AND METHODS

PREVEND and PREVEND IT

The design and principal results of the PREVEND IT¹³ and the PREVEND study have been reported in detail elsewhere. PREVEND IT is part of the ongoing PREVEND study,^{8,24} and subjects for PREVEND IT were recruited from the PREVEND cohort. The PREVEND study was designed to study the impact of albuminuria levels on CV and renal morbidity and

mortality in the general Dutch population. In 1997–1998, the prescreening phase began when all inhabitants aged 28 to 75 years in the city of Groningen ($N = 85,421$) were invited to send in a morning urine sample for measurement of the urinary albumin concentration (UAC) and to complete a questionnaire on demographic characteristics and CV history (Figure 1). Responses were received from 40,856 persons. Based on their UAC, subjects were invited for further study. Of the 40,856 responders, 9966 had a $\text{UAC} \geq 10$ mg/L. Excluded from further study were diabetic subjects ($n = 167$), pregnant women ($n = 60$), and those who declined to participate ($n = 3739$). Two urine samples were collected in a 24-hour period from each of the remaining 6000 subjects. These subjects were invited to the outpatient clinic for testing and further assessment of CV risk factors and CV and renal morbidity. At this stage, subjects with erythrocyturia or leukocyturia, known renal disease, or missing data were excluded. Of the final group of subjects, 3964 had normal UAE (<15 mg/d); 1105 had high-normal UAE (15–30 mg/d); 931 had microalbuminuria (UAE 30–300 mg/d), including 498 with high microalbuminuria (UAE 50–300 mg/d); and 82 had macroalbuminuria (UAE >300 mg/d).²⁶

Formal inclusion criteria for the PREVEND IT study were persistent albuminuria (1 UAC measurement >10 mg/L and ≥ 1 UAE measurement of 15–300 mg/d), blood pressure $<160/100$ mm Hg (threshold for normal blood pressure according to Dutch guidelines at the time of the design of the study²⁷), no use of antihypertensive or lipid-lowering drugs, and total plasma cholesterol <8.0 mmol/L (<5.0 mmol/L in the case of previous myocardial infarction).

Eight hundred sixty-four subjects who fulfilled the inclusion criteria were willing to participate in the study. These subjects were randomized to receive fosinopril 20 mg, fosinopril placebo, pravastatin 40 mg, or pravastatin placebo in a 2×2 factorial design.¹³ The primary end point of PREVEND IT was the incidence of CVEs, defined as CV mortality, nonfatal myocardial infarction or myocardial ischemia, heart failure, peripheral vascular disease, or cerebrovascular attack.

The CVE rate in the PREVEND IT population was $\sim 15\%$. The planned sample size of 450 subjects in each arm (450 fosinopril vs 450 placebo or 450 pravastatin vs 450 placebo, based on the 2×2 factorial design) provided a power of $\sim 80\%$ to detect a significant

difference in the incidence of CVEs between the active-treatment and placebo arms.¹³

Subjects included in PREVEND IT had a mean (SD) age of 51 (2) years, and 65% were male. They had relatively normal systolic and diastolic blood pressure (130 [18]/76 [10] mm Hg) and cholesterol levels (5.8 [1.0] mmol/L). Median UAE was 22.8 (15.8–41.3) mg/d. During follow-up (46 [7] months), the primary end point occurred in 45 (5.2%) subjects, 17 (3.9%) in the fosinopril group ($n = 431$) and 28 (6.5%) in the placebo group ($n = 433$) (hazard ratio, 0.60; 95% CI, 0.33–1.10; $P = 0.098$, log-rank test). Because of the 2×2 factorial design, patients in both the fosinopril and placebo groups also may have received pravastatin (Figure 1, Table I). In post hoc analysis, this effect differed in subjects with a UAE >50 mg/d who received fosinopril, whereby a relative risk reduction in CVEs of up to 60% was observed (5.2% vs 13.0%; $P = \text{NS}$). Also, a significantly worse prognosis for event-free survival was associated with a UAE >50 mg/d in subjects receiving placebo ($P = 0.008$). The primary end point occurred in 21 (4.8%) subjects in the pravastatin group ($n = 433$) and 24 (5.6%) subjects in the placebo group ($n = 431$) (hazard ratio, 0.87; 95% CI, 0.49–1.57; $P = \text{NS}$).¹³

Study Design

The present study was a cost-effectiveness analysis with a focus on net costs per life-year gained (LYG).^{28,29} In all calculations, fosinopril treatment was assumed after detection of a UAE above the defined threshold. In the baseline analysis, this threshold was set at 15 mg/d. For efficacy, subjects receiving fosinopril ($n = 431$) were compared with subjects receiving placebo ($n = 433$), regardless of the receipt of pravastatin treatment in the 2×2 factorial design. This approach optimized the number of subjects included in the economic analysis. In the sensitivity analysis, cost-effectiveness was analyzed based on age (>50 and >60 years¹³), and the cutoff for albuminuria was varied (>30 and >50 mg/d).

The study adopted the Dutch health care perspective and focused on the costs of hospital resource use for CVEs: hospitalizations, diagnostic tests, and therapeutic procedures. Additionally, the estimated costs of screening and fosinopril treatment were included. Patient-level data on resource use were collected over the full period of study follow-up. All costs were expressed in 2002 euros.

Figure 1. Flow chart of the design and subjects experiencing the primary end point (a cardiovascular event [CVE]) of PREVENT IT (Prevention of RENal and Vascular ENDstage Disease Intervention Trial). UAC = urinary albumin concentration; UAE = urinary albumin excretion; RCT = randomized clinical trial.

Table I. Primary end points of the Prevention of REnal and Vascular ENdstage Disease Intervention Trial.

Primary End Point	Fosinopril (n = 431)	Placebo (n = 433)
Cardiovascular death	3	3
Nonfatal myocardial infarction	12	11
Percutaneous transluminal coronary angioplasty	5	4
Coronary arterial bypass grafting	4	2
Heart failure	0	2
Peripheral artery disease	1	2
Cerebrovascular disease (stroke)	1	10
Total cardiovascular events	17	28

Table II. Costs of screening for albuminuria in the general Dutch population, based on the Prevention of REnal and Vascular ENdstage Disease study.

Screening Stage	Cost, Year-2002 €
Prescreening (N = 85,421)	282,727
Screening (n = 6000)	500,909
Identification of 1 person with a UAE above the specified threshold	
>50 to <300 mg/d (n = 498)	1574
>30 to <300 mg/d (n = 931)	842
>15 to <300 mg/d (n = 2036)	385

UAE = urinary albumin excretion.

Costs

Screening costs were estimated based on data from the PREVEND study (Table II). The costs of inviting 85,421 persons to take part in the prescreening program and of prescreening 40,856 persons were €62,700 for apparatus, €76,800 for administration, €61,800 for laboratory materials, and €81,400 for personnel. The costs of the subsequent screening program were €73,600 for apparatus, €9100 for administration, €90,000 for laboratory materials, and €328,200 for personnel. Personnel costs related to research (epidemiologists and statisticians) were excluded, as these would not be part of the routine screening program for which cost-effectiveness was estimated. The total costs of the prescreening and subsequent screening programs were €783,600. The costs of identifying 1 person with a UAE between 15 and 300 mg/d were estimated at €385. Limitation of treatment to those with a UAE of >30 and >50 mg/d was associated with a higher cost of identifying 1 such person (€842 and €1574, respectively).

The costs of fosinopril were based on actual consumption during the study follow-up period. The costs of general practitioner (GP) visits (€18/visit) and pharmacy charges associated with dispensing the prescription (€6/prescription per 3 months) were also taken into account. No visits to the GP were assumed for adverse effects of fosinopril. The costs of medication were obtained from the 2002 Dutch Pharmacotherapeutic Guidelines.³⁰

Hospital costs associated with diagnostic and therapeutic procedures for CVEs corresponding to the primary end point were derived by multiplying resource use by unit costs taken from Dutch tariffs.³¹ Daily inpatient costs on a regular ward were €199 in a general hospital, €279 in an academic hospital, and €889 for an intensive care unit, based on Dutch reference prices for pharmacoeconomic evaluations.^{32,33} These costs included specialist, resident physician, and nursing fees; laundry; nutrition; accommodation and cleaning; overhead; and equipment.³² Costs for outpatient visits were €40 in a general hospital and €70 in an academic hospital.³³ Patient-specific costs for medications other than the study drugs received during hospitalization were not explicitly included (mean costs for nonspecific patient medications are incorporated into the cost of the inpatient hospital day). Every subject with a reported CVE had different total hospital costs, depending on individual diagnostic and therapeutic procedures, length of hospital stay, and number of visits to the outpatient clinic.

Cost-Effectiveness Analysis

The cost-effectiveness ratio (CER) was expressed in net costs per LYG. Net costs resulted from the costs of screening and fosinopril treatment minus the benefits of averted costs related to averted events (ie, screening/treating vs no screening/“doing nothing”). Calculation of LYG was based on losses in the remaining

life expectancy of subjects with CVEs in both groups (fosinopril and placebo). Loss in remaining life expectancy after a CVE was estimated using a Dutch adaptation of data from the Framingham Study² and standard Dutch life tables (data for 1998–2002, Central Bureau of Statistics).³⁴ Table III lists these assumptions (interpolations were used for ages between those presented). Monetary amounts and LYG were discounted at 4%, according to Dutch guidelines for pharmacoeconomic research.³⁵

Statistical Analysis

Bootstrapping of PREVEND IT data (10,000 replications) was used to derive 95% CIs for the CER and threshold probabilities.^{36–39} The bootstrap calculation was performed with S-Plus version 7.0 software (Insightful Corporation, Seattle, Washington). To describe the uncertainty in estimates of the CER, we constructed acceptability curves.⁴⁰ These curves show probabilities that the screen-and-treat intervention is acceptable given a specific threshold, above which the CER is considered unfavorable and below which it is considered favorable. In cost-effectiveness acceptability analyses, we report the median CER and the percentage corresponding to €20,000/LYG, as this figure is the only published threshold for The Netherlands (no formal threshold exists in The Netherlands for cost per quality-adjusted life-year [QALY]).⁴¹ However, this threshold is subject to controversy and its use should be interpreted with caution.^{42,43}

Sensitivity Analysis

Sensitivity analysis was directed at the performance of the intervention in various subgroups and the potential for targeted implementation. For example, analyses were done for the screening of specific age groups (in particular, >50 years and >60 years). Additionally, the post hoc analyses were conducted on subjects with a UAE >30 mg/d and those with a UAE >50 mg/d, using the specific costs of identifying 1 person with a UAE above these thresholds. Differences in the results of the sensitivity and baseline analyses were related to the effectiveness of fosinopril in the various subgroups and the costs required to identify 1 person eligible for fosinopril treatment.

RESULTS

The primary end point in the PREVEND IT trial occurred 17 times in the fosinopril group (16 men,

Table III. Remaining life expectancy at various ages in the general population* and in subjects who have had a cardiovascular event (CVE).[†]

Age	General Population, y	After a CVE, y
Men		
50 years	27.8	15.9
60 years	19.3	12.3
70 years	12.1	8.8
80 years	6.8	5.3
Women		
50 years	32.4	20.3
60 years	23.5	16.1
70 years	15.4	11.0
80 years	8.7	7.0

*Dutch life tables.³⁴

[†]Framingham life tables² adapted to the Dutch population.

1 woman) and 28 times in the placebo group (20 men, 8 women) (Figure 1, Table I).

Costs

In the baseline analysis, the costs of CVEs calculated from the clinical trial were €207 and €148 per subject in the fosinopril and placebo groups, respectively (Table IV). Although fewer events occurred in the fosinopril group, per-person costs in that group were higher due to more costly treatments per event (more percutaneous transluminal coronary angioplasty and coronary artery bypass grafting procedures were performed in this group) (Table I). However, differences in the costs of CVEs between the 2 groups were not statistically significant. The costs of research were excluded from this analysis.

The calculated costs were applied to the screen-and-treat and no-screening strategies (Table IV). Adding the estimated costs of €207 for CVEs, €1296 for fosinopril treatment (including GP and pharmacist costs), and screening costs of €385 (36% for pre-screening and 64% screening) resulted in total estimated costs of €1889 per person (€1809 if discounted). No further screening or treatment costs were considered for the no-screening option, resulting in a total cost of €148 per person (€139 if discounted) (Table IV). Therefore, the difference in discounted costs between the screen-and-treat approach and the no-screening approach was estimated at €1670 per person.

Table IV. Estimated mean costs per person for 2 strategies: screening for albuminuria and treating with fosinopril compared with no screening.

Cost Component	Estimated Mean Costs, Year-2002 €		
	Screen and Treat	No Screening	Incremental
Cardiovascular events	207	148	59
Procedures	113	68	45
Hospital contacts	94	80	14
Intervention	1682	0	1682
Fosinopril	1002	0	1002
GP and pharmacist fees	295	0	295
Screening*	385	0	385
Total costs			
Undiscounted	1889	148	1741
Discounted	1809	139	1670

GP = general practitioner.

*Costs of identifying 1 person with albuminuria in the baseline analysis.

Baseline Cost-Effectiveness Analysis

The higher CVE rate in the placebo group compared with the fosinopril group (6.5% vs 3.9%, respectively) translated into an estimated mean number of 0.28 discounted life-year lost per person not using fosinopril, compared with 0.18 year in those receiving fosinopril. These figures were applied to the no-screening and screen-and-treat options, with the result that screen-and-treat was estimated to result in 0.10 LYG per person in the baseline analysis (slightly >1 month).

In the baseline analysis, estimated mean cost-effectiveness was €16,700 per LYG. Figure 2 shows the corresponding scatterplots for the 10,000 bootstrap replicates of net cost and effect in the cost-effectiveness plane, the estimated mean, and the 95% CI. Results are spread across the first and fourth quadrant of the cost-effectiveness plane. The estimated cost-effectiveness was below the informal Dutch threshold of €20,000/LYG.

Additionally, we determined the probability that the CER would be above or below various thresholds for maximum willingness to pay for 1 LYG (Figure 3). For 50% of the bootstrap replicates in the baseline analysis, estimated cost-effectiveness was below €16,500/LYG. For a maximum acceptable cost-effectiveness of €20,000, the probability of the screen-and-treat option being cost-effective was estimated at 59% (Figure 3, Table V).

Sensitivity Analysis

In the sensitivity analysis, we analyzed the cost-effectiveness of limiting treatment to only those subjects with a UAE >30 or >50 mg/d (Figures 2 and 3; Table V). Estimated median CERs for those subjects were lower compared with the baseline analysis (€12,000, €7000, and €16,500 for UAE >30, UAE >50, and baseline, respectively), and threshold probabilities increased to >90% for UAE >50 mg/d. Furthermore, the estimated median cost-effectiveness was lower for screening and treating subjects aged >50 years and >60 years compared with screening all subjects in the baseline analysis.

DISCUSSION

This study analyzed the cost-effectiveness of using fosinopril for the primary prevention of CVEs in subjects with albuminuria (UAE >15 mg/d) from the Dutch health care perspective. We estimated a mean CER for screening and subsequent fosinopril treatment (vs no screening) of €16,700/LYG. With a maximum acceptable cost-effectiveness for The Netherlands of €20,000/LYG, our point estimate would be considered cost-effective. Analysis indicated an estimated 59% probability of the screen-and-treat strategy being cost-effective. Although this percentage was not statistically significant for favorable cost-effectiveness, screening for albuminuria and subsequent fosinopril

Figure 2. Cost-effectiveness of screening for albuminuria and subsequent fosinopril treatment compared with no screening (A) in all subjects with microalbuminuria (urinary albumin excretion [UAE] >15 mg/d) (cost-effectiveness ratio [CER] = €16,700/life-year gained [LYG]) and in sensitivity analyses in (B) subjects with UAE >30 mg/d (CER = €12,000/LYG) and (C) subjects with UAE >50 mg/d (CER = €6900/LYG). Scatter-plots represent 10,000 replicates per analysis using the bootstrap method. Any cost-effectiveness plane contains net costs in euros (ΔC) on the x axis and LYG as effects (ΔE) on the y axis. Dotted lines are 95% CIs, the dashed line is the estimated mean, and the solid line is the informal Dutch pharmacoeconomic threshold (€20,000/LYG).

treatment appears to be worth consideration from a pharmacoeconomic perspective. It should be remembered that our study was designed to be hypothesis generating, and our results require further investigation and confirmation.

In sensitivity analyses, we investigated how the cost-effectiveness varied by subgroup. In particular, in subjects aged >50 years and >60 years, a relatively more favorable cost-effectiveness was estimated for a UAE

cutoff of >15 mg/d. Also, limiting treatment to those subjects with a UAE >30 or >50 mg/d was associated with improved cost-effectiveness.

Our study did not explicitly include assumptions about the specificity and sensitivity of the testing sequence during screening (1 UAC measurement and two 24-hour UAE measurements), although testing performance is implicitly incorporated in the analysis. Prescreening through measurement of UAC in a spot

Figure 3. Cost-effectiveness acceptability curves for screening for albuminuria and subsequent fosinopril treatment compared with no screening (A) in all subjects (baseline) and in sensitivity analyses in (B) subjects with urinary albumin excretion (UAE) >30 mg/d and (C) subjects with UAE >50 mg/d. Any curve represents the probability of the screen-and-treat approach being acceptable over a range of cost-effectiveness thresholds for decision-makers' willingness to pay. The broken line on the x axis indicates the cost-effectiveness ratio of €20,000/life-year gained (informal Dutch pharmacoeconomic threshold), and the broken lines on the y axis indicate 50% and 95% of the probability of acceptance.

Table V. Median cost-effectiveness ratio (CER) and the probability of acceptable cost-effectiveness given a threshold of €20,000 per life-year gained in the baseline and sensitivity analyses.

Analytic Group	Median CER, €	Probability of Acceptable Cost-Effectiveness
All subjects (baseline)	16,500	0.59
UAE >30 mg/d	12,000	0.72
UAE >50 mg/d	7000	0.91
Subjects aged >50 y	13,600	0.63
Subjects aged >60 y	6300	0.80

UAE = urinary albumin excretion.

morning urine sample is satisfactorily predictive of the UAE (specificity 85%). Some subjects with elevated albumin levels were missed (estimated sensitivity 85%), but prescreening kept the burden and costs of population screening as low as possible.⁴⁴ If a better screening procedure were to become available, the costs of identifying 1 person with a UAE above a certain threshold would be lower and would probably result in a more favorable cost-effectiveness outcome.

Only 1 study was found in the literature comparable to ours. This study investigated initial dipstick screening for proteinuria in a general population, with follow-up tests to confirm proteinuria and initiate ACE-inhibitor treatment.⁴⁵ The study team's method of screening for proteinuria yielded fewer subjects than our method of screening for albuminuria, which explains their higher CERs (US \$53,370–\$282,800/QALY gained). In particular, because the prevalence of proteinuria was <1%, their approach required screening of many individuals to identify 1 case. In data from the PREVEND study,^{24,25} we found a prevalence of proteinuria of 1.1%, similar to that in the study by Boulware et al. However, the prevalence of a UAE >15 mg/d was 12.1%,²⁶ on which our current economic study is based. There were also differences between Boulware's and our approach in relation to health care systems and specific implementations (GP-screening based vs population-screening based).⁴⁵ Of greatest importance, Boulware et al took into account only those savings that applied to the prevention of death from all causes and end-stage renal disease, whereas we focused on the effect of ACE inhibition in preventing CVEs. Inclusion of fosinopril treatment for subjects with overt proteinuria on screening instead of those with a UAE between 15 and 300 mg/d would further improve the cost-effectiveness of screening, given the favorable cost-effectiveness of ACE-inhibitor therapy seen in subjects with proteinuria.⁴⁶

Cost-effectiveness of ACE-inhibitor therapy in non-proteinuric populations has been studied. Bjorholt et al¹⁸ conducted a substudy of Swedish participants in the Heart Outcomes Prevention Evaluation trial to estimate the cost-effectiveness of ramipril treatment for subjects with CVD or diabetes. Their findings indicated net costs of €1940 to €5300/LYG. That estimate included treatment only; costs of screening were not considered. Based on our data, we estimated the cost-effectiveness of fosinopril treatment in subjects with

albuminuria at €12,700/LYG (from the baseline analysis).

The PREVEND IT study was directed at otherwise healthy people (no subjects with diabetes, high cholesterol levels, or high blood pressure); therefore, concomitant drug use was expected to be relatively low and was not considered in the study.

The strength of our study is that it combines population-based data on the prevalence of albuminuria with outcomes of treatment in a subsection of that population. Also, the study was based on documented events occurring during follow-up of the PREVEND IT study, minimizing the number of assumptions required to perform the entire analysis. The inherent limitation of our study is that it lacks data beyond the specified end point, such as nursing home care for stroke, rehabilitation after acute events, and potential rehospitalizations, with the corresponding costs (lifetime costs of events were not taken into account in our analyses). Therefore, the cost-effectiveness may be even more favorable. Given the limited period of follow-up in the PREVEND IT study, lifetime health gains were modeled using Dutch data on remaining life expectancy and the Framingham life tables.

A major drawback to the PREVEND IT study was that the apparent difference between lowering UAE and the incidence of CVEs was not statistically significant, possibly because of the limited number of subjects included. But, if the PREVEND IT study, which was performed on an intent-to-treat basis, were instead performed on a per-protocol basis, the relationship between UAE and CVEs would be statistically significant. The per-protocol analysis itself can be provided on request. A larger sample size with longer follow-up (resulting in more events) might also have resulted in a statistically significant difference. Finally, this study was limited to a 1-time screening program; inclusion of subsequent screening(s) might result in less favorable cost-effectiveness. In general, cost-effectiveness analysis based on clinical trials has its limitations; in particular, the clinical trial does not reflect the real world, and the time frame is limited.

Further work using our approach should involve the combination of a CVE and the progression of renal disease. For that purpose, a Markov model could be developed with stages corresponding to albuminuria levels, which would offer the opportunity to simulate a periodic screening procedure in the general population. Such models have been developed with a

focus on renal disease in subjects with diabetes,^{21,47} but they have not formally included CV risks. Also, such a Markov model would allow an investigation of cost-effectiveness that included subsequent screening(s) and long-term CV and renal outcomes.

The PREVEND and PREVEND IT studies were performed in a predominantly white population (>95% of subjects). This may theoretically limit the external validity of our analysis. However, in nonwhite subjects, the prevalence of microalbuminuria, as well as the incidence of CVD, has been shown to be substantially higher than in white subjects.^{48–51} We believe that screening for albuminuria and subsequent treatment with an ACE inhibitor may be more cost-effective in populations with larger proportions of black individuals. In our study, we did not include the cost of complications of fosinopril treatment. Adverse events (particularly cough) were reported by 3.5% (29) of subjects in PREVEND IT.¹³ As these adverse events were mild, they did not influence our cost-effectiveness estimate. The possibility of these complications leading to noncompliance was included in our study design.

CONCLUSIONS

This analysis from a Dutch health care perspective suggests the potential favorable cost-effectiveness of a screening program for albuminuria in the general population. The estimated cost-effectiveness of approximately €16,700/LYG for subjects with a UAE >15 mg/d was below the Dutch threshold for cost-effectiveness. Cost-effectiveness might be further improved by limiting screening to predefined subgroups (eg, by age, by limiting treatment to those with higher albuminuria levels). Further research is needed to evaluate our findings in other settings using a longer time horizon, including periodically repeated screening and lifetime cost estimates.

ACKNOWLEDGMENTS

PREVEND IT was financed by Netherlands Heart Foundation, The Hague, The Netherlands, and an unrestricted grant from Bristol-Myers Squibb Company, New York, New York. Dr. Atthobari is a recipient of the Ubbo Emmius scholarship funded by the University of Groningen. Dr. Asselbergs was a research fellow of Netherlands Heart Foundation. Mr. Boersma is a research fellow of the Dutch Kidney Foundation, Bussum, The Netherlands. None of the sponsors of our research played a role in the design or conduct of

this study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

The authors thank all the PREVEND IT investigators, including those from the University of Groningen and University Hospital Groningen, The Netherlands: E.M. Stuveling, Department of Internal Medicine; J.C. Verhave, Department of Nephrology; S.J. Pinto-Sietsma, Department of Nephrology; A.H. Boonstra, Department of Nephrology; and L.J. Wagenaar, Department of Cardiology.

The authors also acknowledge the contributions to PREVEND IT of the following individuals. Steering Committee, University of Groningen and University Hospital Groningen: W.H. van Gilst (principal investigator), Departments of Clinical Pharmacology and Cardiology; D.J. van Veldhuisen, Department of Cardiology; P.E. de Jong, Department of Nephrology; D. de Zeeuw, Department of Clinical Pharmacology; A.J. van Boven, Department of Cardiology; H.L. Hillege, Trial Coordination Center; W.M.T. Janssen, Department of Nephrology; G.F.H. Diercks, Department of Cardiology; and F.W. Asselbergs, Departments of Clinical Pharmacology and Cardiology. Endpoint Committee: F.W.A. Verheugt (chairman), Department of Cardiology, Academic Hospital, Nijmegen, The Netherlands; L. Schrijvers, Department of Cardiology, Martini Hospital, Groningen, The Netherlands; and T. Kremer Hovinga, Department of Nephrology, Martini Hospital, Groningen, The Netherlands. Safety and Data Monitoring Committee: B. Pitt (chairman), Division of Cardiology, University of Michigan, Ann Arbor; and J. Shepherd, Department of Pathological Biochemistry, Royal Infirmary, Glasgow, United Kingdom. Data management: R.J. Bieringa, Trial Coordination Center, Thoraxcenter, Academic Hospital, Groningen, The Netherlands. Statistical support: A.H. Zwinderman, Academic Medical Center, Amsterdam, The Netherlands.

REFERENCES

1. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part I: General considerations, the epidemiologic transition, risk factors and impact of urbanization. *Circulation*. 2001;104:2746–2753.
2. Peeters A, Mamun AA, Willekens F, Bonneux L. A cardiovascular life history. A life course analysis of the original Framingham Heart Study cohort. *Eur Heart J*. 2002;23:458–466.

3. Reitsma JB, Dalstra JA, Bonse GJ, et al. Cardiovascular disease in the Netherlands, 1975 to 1995: Decline in mortality, but increasing numbers of patients with chronic conditions. *Heart*. 1999;82:52-56.
4. Gerstein HC, Mann JF, Yi Q, et al, for the HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286:421-426.
5. Anavekar NS, Gans DJ, Berl T, et al. Predictors of cardiovascular events in patients with type 2 diabetic nephropathy and hypertension: A case for albuminuria. *Kidney Int Suppl*. 2004; 92:S50-S55.
6. Wachtell K, Ibsen H, Olsen MH, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: The LIFE study. *Ann Intern Med*. 2003;139: 901-906.
7. Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, et al. Urinary albumin excretion. An independent predictor of ischemic heart disease. *Arterioscler Thromb Vasc Biol*. 1999; 19:1992-1997.
8. Hillege HL, Fidler V, Diercks GF, et al, for the Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in the general population. *Circulation*. 2002; 106:1777-1782.
9. Romundstad S, Holmen J, Kvenild K, et al. Microalbuminuria and all-cause mortality in 2,089 apparently healthy individuals: A 4.4-year follow-up study. The Nord-Trøndelag Health Study (HUNT), Norway. *Am J Kidney Dis*. 2003;42:466-473.
10. de Jong PE, Hillege HL, Pinto-Sietsma SJ, de Zeeuw D. Screening for microalbuminuria in the general population: A tool to detect subjects at risk for progressive renal failure in an early phase? *Nephrol Dial Transplant*. 2003;18:10-13.
11. Yusuf S, Sleight P, Pogue J, et al, for the Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients [published corrections appear in *N Engl J Med*. 2000;342: 748 and *N Engl J Med*. 2000;342:1376]. *N Engl J Med*. 2000;342:145-153.
12. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet*. 1997;349:1857-1863.
13. Asselbergs FW, Diercks GF, Hillege HL, et al, for the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation*. 2004;110:2809-2816.
14. Boersma C, Attobari J, Gansevoort RT, et al. Pharmacoeconomics of angiotensin-II antagonists in type 2 diabetic patients with nephropathy; implications for decision-making. *Pharmacoeconomics*. In press.
15. Nordmann AJ, Krahn M, Logan AG, et al. The cost effectiveness of ACE inhibitors as first-line antihypertensive therapy. *Pharmacoeconomics*. 2003; 21:573-585.
16. Hart WM, Rubio-Terres C, Pajuelo F, Gonzalez Juanatey JR. Cost-effectiveness of the treatment of heart failure with ramipril: A Spanish analysis of the AIRE study. *Eur J Heart Fail*. 2002;4:553-558.
17. Szucs TD. Pharmacoeconomics of angiotensin converting enzyme inhibitors in heart failure. *Am J Hypertens*. 1997;10:272S-279S.
18. Bjorholt I, Andersson FL, Kahan T, Ostergren J. The cost-effectiveness of ramipril in the treatment of patients at high risk of cardiovascular events: A Swedish sub-study to the HOPE study. *J Intern Med*. 2002;251: 508-517.
19. Brandle M, Davidson MB, Schriger DL, et al. Cost effectiveness of statin therapy for the primary prevention of major coronary events in individuals with type 2 diabetes. *Diabetes Care*. 2003;26:1796-1801.
20. Malik IS, Bhatia VK, Kooner JS. Cost effectiveness of ramipril treatment for cardiovascular risk reduction. *Heart*. 2001;85:539-543.
21. Golan L, Birkmeyer JD, Welch HG. The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. *Ann Intern Med*. 1999;131: 660-667.
22. Palmer AJ, Annemans L, Roze S, et al. Cost-effectiveness of early irbesartan treatment versus control (standard antihypertensive medications excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers) or late irbesartan treatment in patients with type 2 diabetes, hypertension, and renal disease. *Diabetes Care*. 2004;27:1897-1903.
23. Boulware LE, Jaar BG, Tarver-Carr ME, et al. Screening for proteinuria in US adults: A cost-effectiveness analysis. *JAMA*. 2003;290:3101-3114.
24. Hillege HL, Janssen WM, Bak AA, et al, for the PREVEND Study Group. Microalbuminuria is common, also in a nondiabetic nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med*. 2001;249:519-526.
25. Diercks GF, Janssen WM, van Boven AJ, et al. Rationale, design, and baseline characteristics of a trial of prevention of cardiovascular and renal disease with fosinopril and pravastatin in nonhypertensive, nonhypercholesterolemic subjects with microalbuminuria (the Prevention of Renal and Vascular Endstage Disease Intervention Trial [PREVEND IT]). *Am J Cardiol*. 2000;86:635-638.
26. Pinto-Sietsma SJ, Janssen WM, Hillege HL, et al. Urinary albumin excretion is associated with renal

- functional abnormalities in a nondiabetic population. *J Am Soc Nephrol*. 2000;11:1882-1888.
27. Walma EP, Grundmeijer HGLM, Thomas S, et al. NHG Standaard hypertensie, eerste herziening. (Dutch College of General Practitioners Guideline "Hypertension," first revision [in Dutch]). *Huisarts en Wetenschap*. 1997;40:598-617.
 28. Gold MR, Siegel JE, Russel LB, Weinstein MC. Cost-effectiveness in health and medicine. New York, NY: Oxford University Press; 1996.
 29. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ*. 1994;3:309-319.
 30. Health Care Insurance Board. *Dutch Pharmacotherapeutic Guidelines* [in Dutch]. Amstelveen, The Netherlands: 2002.
 31. College Tarieven Gezondheidszorg. *Dutch Tariff Book for Medical Specialists* [in Dutch]. Available at: www.ctgzorg.nl. Accessed January 10, 2004.
 32. Oostenbrink JB, Buijs-Van der Woude T, van Agthoven M, et al. Unit costs of inpatient hospital days. *Pharmacoeconomics*. 2003;21:263-271.
 33. Oostenbrink JB, Koopmanschap MA, Rutten FF. Standardisation of costs: The Dutch Manual for Costing in economic evaluations. *Pharmacoeconomics*. 2002;20:443-454.
 34. Dutch Central Bureau of Statistics. Available at: <http://statline.cbs.nl>. Accessed January 10, 2004.
 35. Health Care Insurance Board. Dutch Guidelines for Pharmacoeconomic Research. Available at: http://www.ispor.org/PEguidelines/source/PE_guidelines_english_Netherlands.pdf. Accessed February 24, 2006.
 36. Barber JA, Thompson SG. Analysis of cost data in randomized trials: An application of the non-parametric bootstrap. *Stat Med*. 2000;19:3219-3236.
 37. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: Recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. *Annu Rev Public Health*. 2002; 23:377-401.
 38. Cook JR, Heyse JF. Use of an angular transformation for ratio estimation in cost-effectiveness analysis. *Stat Med*. 2000;19:2989-3003.
 39. Klok RM, Arents NL, de Vries R, et al. Economic evaluation of randomized trial comparing *Helicobacter pylori* test-and-treat and prompt endoscopy strategies for managing dyspepsia in a primary-care setting. *Clin Ther*. 2005;27:1647-1657.
 40. Lothgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. *Health Econ*. 2000;9:623-630.
 41. Zwart-van Rijkom JE, Leufkens HG, Busschbach JJ, et al. Differences in attitudes, knowledge and use of economic evaluations in decision-making in The Netherlands. The Dutch results from the EUROMET Project. *Pharmacoeconomics*. 2000;18:149-160.
 42. Bos JM, Postma MJ. Using pharmacoeconomics for policy making: Is rational decision making enhanced by applying thresholds for cost-effectiveness? *Expert Rev Pharmacoeconom Outcomes Res*. 2004;4:247-250.
 43. Owens DK. Interpretation of cost-effectiveness analyses. *J Gen Intern Med*. 1998;13:716-717.
 44. Gansevoort RT, Verhave JC, Hillege HL, et al, for the PREVEND Study Group. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. *Kidney Int Suppl*. 2005;94:S28-S35.
 45. Gansevoort RT, de Jong PE, Postma MJ. Cost-effectiveness of screening for proteinuria. *JAMA*. 2004;291: 1442-1443.
 46. van Hout BA, Simeon GP, McDonnell J, Mann JF. Economic evaluation of benazepril in chronic renal insufficiency. *Kidney Int Suppl*. 1997;63:S159-S162.
 47. Rodby RA, Chiou CF, Borenstein J, et al, for the Collaborative Study Group. The cost-effectiveness of irbesartan in the treatment of hypertensive patients with type 2 diabetic nephropathy. *Clin Ther*. 2003;25: 2102-2119.
 48. Jones CA, Francis ME, Eberhardt MS, et al. Microalbuminuria in the US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 2002;39:445-459.
 49. Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: Implications of sex and race. *J Am Soc Nephrol*. 2002;13: 1034-1039.
 50. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. *Arch Intern Med*. 1997;157:1413-1418.
 51. Toto RD. Proteinuria and hypertensive nephrosclerosis in African Americans. *Kidney Int Suppl*. 2004;92:S102-S104.

Address correspondence to: Cornelis Boersma, MSc, Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands. E-mail: c.boersma@rug.nl

Alternate correspondence: Maarten Postma, PhD, same address as above. E-mail: m.j.postma@rug.nl