CHAPTER 7

Cost-effectiveness of screening for albuminuria with subsequent fosinopril treatment to prevent cardiovascular events: a pharmacoeconomic analysis linked to the PREVEND and PREVEND-IT study

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CHAPTER SEVEN

ABSTRACT

Introduction
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 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€ = 1.01 US$) 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 would increase to 91% if 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 placebo from the Dutch health care perspective. Confirmation from larger multicenter trials is needed.
INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death in many countries [12]. 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 al [21] 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 al [22] found that the use of angiotensin-receptor antagonists in subjects with diabetes was more cost-effective compared to other antihypertensive to improve life expectancy if treatment was started during the early microalbuminuria stage (i.e. UAE >30 mg/d). However, Boulware et al [23] 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 CVE (PubMed; up to 2005; key words: cost-effectiveness, albuminuria, cardiovascular disease. Therefore, the present study aimed to investigate the cost-effectiveness of
screening for albuminuria to prevent CVE with ACE-inhibitor treatment using data from 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 (\(p=ns\)). 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% in pravastatin vs. 5.6% in placebo; Hazard ratio 0.87 [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.

PATIENTS AND METHODS

PREVEND and PREVEND-IT
The design and principal results of PREVEND-IT\[23\] and the Prevention of REnal and Vascular ENdstage Disease \[25\] (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 study. The PREVEND trial 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 of the city of Groningen aged 28 to 75 years (\(n = 85,421\)) 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 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. 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]. These subjects were invited to the outpatient clinic for testing and further assessment of CV risk factors and CV and renal morbidity.

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 study) [27], no use of antihypertensive or lipid-lowering drugs, and total 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. The primary end point of PREVEND-IT was the incidence of CVE, 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 estimated at ~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 ~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] mmHg) 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-1). 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=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=ns).13
CHAPTER SEVEN

Invited to participate (N= 85,421)

Responded via morning spot urine sample (N= 40,856)

UAC > 10 mg/L (N= 9966)

Subjects with diabetes, pregnant women, and subjects who declined to participate were excluded

Clinical measurements, two 24-hour urine collections (N= 6000)

UAE 15-300 mg/d (N= 2036)

Normal blood pressure and cholesterol level (N= 1439)

Gave informed consent to participate in double-blind RCT (2 x 2 factorial design) (N= 864)

PREVEND IT

Randomized to treatment

Fosinopril + Pravastatin (N= 216)

Fosinopril + Placebo (N= 215)

Pravastatin + Placebo (N= 217)

Placebo + Placebo (N= 216)

CVE end point (N= 8)

CVE end point (N= 9)

CVE end point (N= 13)

CVE end point (N= 15)

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

<table>
<thead>
<tr>
<th>Primary End Point</th>
<th>Fosinopril (n = 431)</th>
<th>Placebo (n = 433)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>- percutaneous transluminal coronary angioplasty (PTCA)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>- coronary arterial bypass grafting (CABG)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cerebrovascular disease (stroke)</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Total cardiovascular events</td>
<td>17</td>
<td>28</td>
</tr>
</tbody>
</table>

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 years and >60 years \[^{13}\]), 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.
Costs

Screening costs were estimated based on data from the PREVEND study (Table-2). 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 mg/d 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 pharmacist’s fees (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].

Table-2. Costs of screening for albuminuria in the general Dutch population, based on the Prevention of REnal and Vascular ENdstage Disease study

<table>
<thead>
<tr>
<th>Screening Stage</th>
<th>Costs Year-2002 €</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescreening (n = 85,421 subjects)</td>
<td>282,727</td>
</tr>
<tr>
<td>Screening (n = 6000 subjects)</td>
<td>500,909</td>
</tr>
<tr>
<td>Identification of 1 person with a urinary albumin excretion above the specified threshold</td>
<td></td>
</tr>
<tr>
<td>&gt;50 to &lt;300 mg/d (n = 498 subjects)</td>
<td>1574</td>
</tr>
<tr>
<td>&gt;30 to &lt;300 mg/d (n = 931 subjects)</td>
<td>842</td>
</tr>
<tr>
<td>&gt;15 to &lt;300 mg/d (n = 2036 subjects)</td>
<td>385</td>
</tr>
</tbody>
</table>
Hospital costs associated with diagnostic and therapeutic procedures for CVEs corresponding to the primary end points were derived by multiplying resource use by unit costs taken from Dutch tariffs \cite{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 \cite{32,33}. These costs included specialist, resident physician, and nursing fees; laundry; nutrition; accommodation and cleaning; overhead; and equipment \cite{32}. Costs for outpatient visits were €40 in a general hospital and €70 in an academic hospital \cite{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.

\textit{Table-3. Remaining life expectancy at various ages in the general population* and in subjects who have had a cardiovascular event (CVE).†}

<table>
<thead>
<tr>
<th>Age</th>
<th>General Population, years</th>
<th>After a CVE, years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 years</td>
<td>27.8</td>
<td>15.9</td>
</tr>
<tr>
<td>60 years</td>
<td>19.3</td>
<td>12.3</td>
</tr>
<tr>
<td>70 years</td>
<td>12.1</td>
<td>8.8</td>
</tr>
<tr>
<td>80 years</td>
<td>6.8</td>
<td>5.3</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 years</td>
<td>32.4</td>
<td>20.3</td>
</tr>
<tr>
<td>60 years</td>
<td>23.5</td>
<td>16.1</td>
</tr>
<tr>
<td>70 years</td>
<td>15.4</td>
<td>11.0</td>
</tr>
<tr>
<td>80 years</td>
<td>8.7</td>
<td>7.0</td>
</tr>
</tbody>
</table>

*\textit{Dutch life tables.}^{33}
†\textit{Framingham life tables adapted to the Dutch population.}^{2}
CHAPTER SEVEN

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 Study [2] and standard Dutch life tables (data for 1998–2002, Central Bureau of Statistics) [34]. Table-3 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 [36–38]. The bootstrap calculation was performed with S-Plus version 7.0 software (Insightful corporation, Seattle, WA) Parametric bootstrapping was used, assuming a bivariate normal distribution for mean net costs and mean effect (life-years) [28,39] . 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, 1 woman) and 28 times in the placebo group (20 men, 8 women) (Figure-1, Table-1).

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-4). 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.

Table-4. Estimated mean costs per person for 2 strategies: screening for albuminuria and treating with fosinopril compared with no screening.

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>Estimated Mean Costs (2002 €)</th>
<th>Screen and Treat</th>
<th>No Screening</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedures</td>
<td>113</td>
<td>68</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Hospital contacts</td>
<td>93</td>
<td>80</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosinopril</td>
<td>1296</td>
<td>0</td>
<td>1296</td>
<td></td>
</tr>
<tr>
<td>GP and pharmacist fees</td>
<td>295</td>
<td>0</td>
<td>295</td>
<td></td>
</tr>
<tr>
<td>Screening*</td>
<td>385</td>
<td>0</td>
<td>385</td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undiscounted</td>
<td>1888</td>
<td>148</td>
<td>1740</td>
<td></td>
</tr>
<tr>
<td>Discounted</td>
<td>1808</td>
<td>139</td>
<td>1670</td>
<td></td>
</tr>
</tbody>
</table>

GP = general practitioner.
* Costs of identifying 1 person with albuminuria in the baseline analysis.
The calculated costs were applied to the screen-and-treat and no-screening strategies (Table-4). Adding the estimated costs of €207 for cardiovascular events and €1296 for fosinopril treatment (including GP and pharmacist costs) and screening costs of €385 (36% for prescreening and 64% screening) resulted in estimated costs of €1888 per person (€1808 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-4). Therefore, the difference in discounted costs between the screen-and-treat approach and the no-screening approach was estimated at €1670 per person.

**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-years lost per person not using fosinopril, compared with 0.18 years 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 scatter plots 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 per 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-5).

**Sensitivity Analysis**

In the sensitivity analysis, we analyzed the cost-effectiveness of limiting treatment to only those subjects with a UAE >30 mg/d or >50 mg/d (Figures-2 and 3, Table-5). Estimated median CERs for those subjects were lower compared with the baseline analysis (€12000, €7000 and €16500 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.

Figure-2. Cost-effectiveness of screening for albuminuria and subsequent fosinopril treatment compared with no screening (2A) 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 (2B) subjects with UAE>30 mg/d (CER = €12,000/LYG and (2C) subjects with UAE>50 mg/d (CER = €6900/LYG). Scatter-plot represent 10,000 replicates per analysis using 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% CI, the dashed line is the estimated mean, and the solid line is the informal Dutch pharmacoeconomic threshold (€20,000/LYG).
Table 5. 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.

<table>
<thead>
<tr>
<th>Analytic Group</th>
<th>Median Cost-effectiveness Ratio (€)</th>
<th>Probability of Acceptable Cost-Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects (baseline)</td>
<td>16,500</td>
<td>0.59</td>
</tr>
<tr>
<td>UAE &gt;30 mg/d</td>
<td>12,000</td>
<td>0.72</td>
</tr>
<tr>
<td>UAE &gt;50 mg/d</td>
<td>7000</td>
<td>0.91</td>
</tr>
<tr>
<td>Subjects aged &gt;50 y</td>
<td>13,600</td>
<td>0.63</td>
</tr>
<tr>
<td>Subjects aged &gt;60 y</td>
<td>6300</td>
<td>0.80</td>
</tr>
</tbody>
</table>

CER = cost effectiveness ratio, UAE = urinary albumin excretion

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 CER for screening and subsequent fosinopril treatment (vs placebo) 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 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 mg/d 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 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 one study comparable to ours was found in the literature (PubMed; up to 2005; key words: cost(-)effectiveness, albuminuria, general population). Boulware et al [23] investigated initial dipstick screening for proteinuria in a general population, with follow-up tests to confirm proteinuria and initiate ACE-inhibitor treatment. Their method of screening for proteinuria yielded fewer subjects than
our method of screening for albuminuria, which explains their higher CERs ($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 the PREVEND data, 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% on which our current economic study is based. There were also differences between our and Boulware’s approaches in relation to health care systems and specific implementations (GP-screening-based vs population-screening-based) (reference 45 give more detailed about the difference between our and Boulware study). Most important, 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.

Cost-effectiveness of ACE-inhibitor therapy in nonproteinuric populations has been studied previously. Björholt et al conducted a substudy of Swedish participants in the HOPE 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 points, 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. However, 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 intention-to-treat basis, were instead performed on per-protocol basis, the relationship between UAE and CVEs might 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 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 [20,47], 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 nonwhites 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% of subjects (n=29) in PREVEND-IT [23]. 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.
CHAPTER SEVEN

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 €7000/LYG for subjects with a UAE >50 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.
REFERENCES


CHAPTER SEVEN


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CHAPTER SEVEN


