CHAPTER FIVE

5

Cost-effectiveness of Fosinopril to prevent cardiovascular events in albuminuric subjects; Pharmaco-economic analysis linked to the PREVEND Intervention Trial (PREVEND-IT)

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Abstract

Background Cardiovascular disease (CVD) is one of the leading causes of death in many countries. Many studies have proven secondary prevention to be cost-effective, but only a few reports thus far proved cost-effectiveness in primary prevention, in particular with respect to nephrologic markers.

Objective To estimate cost-effectiveness of screening the general population for elevated albumin levels with subsequent fosinopril treatment to prevent cardiovascular events. The PREVEND-IT (Prevention REnal and Vascular ENdstage Disease Intervention Trial) was a single centre, double blind, randomised placebo-controlled trial with a two-by-two factorial design to assess the effects of fosinopril 20 mg and pravastatin 40 mg on cardiovascular events in 864 subjects with a urine albumin excretion (UAE) in the range of 15-300mg/day, blood pressure < 160/100 mmHg and plasma cholesterol level < 8.0 mmol/l. Next to the individual data of the PREVEND-IT study, observational data from the larger PREVEND-study were used. Evaluation of treatment was based on the PREVEND-IT study, whereas the screening part of our analysis was primarily based on the observational data gathered among the trial participants and beyond. Cost-effectiveness estimates were produced for the Dutch population, concerning a screening program based in the general community.

Intervention and mean outcome measures The intervention concerned involves community-based screening for elevated albumin levels, with subsequent fosinopril treatment to prevent cardio-vascular events. Cost-effectiveness was expressed in net costs per life-year gained (LYG) in the baseline and (stochastic) sensitivity analysis.

Results Cardiovascular events occurred in 45 (5.2%) subjects included in PREVEND-IT. Patients treated with fosinopril showed a 40% lower incidence of cardiovascular events than patients in the placebo group (3.9% versus 6.5%, respectively, p=0.098). Cost-effectiveness of screening for elevated albuminuria was €16,710/LYG (ranging from €6,100 to €25,400 in sensitivity analysis). Stochastic analysis indicated that the probability of cost-effectiveness below the suggested Dutch threshold for cost-effectiveness of €20,000 per LYG is 61% in the baseline, increasing to 92% if only those subjects are treated with fosinopril showing a UAE in the range of 50-300 mg/day. Also, limiting the screening to only those aged 50 and over improved cost-effectiveness considerably.

Conclusions Screening the general population for elevated albuminuria and subsequent treatment with fosinopril of those found positive may well be cost-effective due to preventing cardiovascular events.

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death in many countries[1-2]. In the Netherlands, CVD accounts for about 11% of all health care costs [3]. Various trials demonstrated the health benefits connected with treatments to prevent CVD. Many studies have proven secondary prevention to be cost-effective [4-7], but only a few reports thus far have investigated cost-effectiveness in primary prevention, in particular with respect to nephrologic markers [8-9].

Primary prevention based on albumin level measurements in the general community presents one option, to be investigated in this paper. One recent paper by Boulware *et al* in this journal addressed exactly this issue for a primary-care based screening in the USA [10]. However – as already indicated in our letter to the editor of the *JAMA* [11] - we argue that the approach chosen by Boulware *et al*[10] of economically analysing screening for dipstick proteinuria with follow-up angiotensin-converting enzyme (ACE) inhibitor treatment to avert renal damage should be extended. In particular, the approach should comprise (1) micro-albuminuric subjects detected by the screening and (2) prevention of CVD-events for such subjects.
Because the incidence of proteinuria was less than 1% in the study by Boulware *et al*, their approach requires screening of many individuals to find one case. Based on Dutch data, we found a prevalence of 0.6% for proteinuria, similar to Boulware et al. [12]. However, the prevalence of micro-albuminuria was substantially higher at 5.5%, and significantly less individuals are to be screened (and costs made) to find one subject.
PREVEND-IT (Prevention of REnal and Vascular ENdstage Disease Intervention Trial)[13] was conducted as a single centre Dutch study, in a two-by-two factorial design to assess the ability of the ACE-inhibitor fosinopril and the HMG CoA Reductase Inhibitor pravastatin to reduce the incidence of cardiovascular events in subjects with albuminuria. Patients treated with fosinopril showed a 40% lower incidence of the primary endpoint on CVD-events than patients in the placebo group.
This paper investigates whether screening for micro-albuminuria is worthwhile from a pharmacoeconomic perspective, based on observational data of the PREVEND-study[14-15] and trial-gathered data in the PREVEND-IT study [12-13].

Methods

The design and principal results of the PREVEND-IT-trial have been reported in detail elsewhere.[12,13] Briefly, the PREVEND-IT-trial is part of the ongoing PREVEND study [14-15]. PREVEND was designed to study the impact of elevated albuminuria levels on cardiovascular and renal morbidity and mortality in the general population. In 1997-1998 the pre-screening phase started, in which all inhabitants of the city of Groningen (North of the Netherlands), aged 28 - 75 years (n=85,421), were asked to send in a morning urine sample for measurement of the urinary albumin concentration (UAC) and to fill out a short questionnaire on demographic and cardiovascular history. Responses in this pre-screening phase were received from 40,856 persons. All subjects with an UAC > 10 mg/l (n=7,768) in their morning urine, together with a randomly selected control group with non-elevated albumin concentrations (< 10 mg/l; n=3,395), were subse-

quently invited to the outpatient clinic for extended testing and further assessment of cardiovascular risk factors and detailed inventory of cardiovascular and renal morbidity. Subjects who reported pregnancy or insulin-using diabetics were excluded. A total of 8,592 subjects completed the screening program, in which amongst others two further urine samples were collected for accurate measurement of the 24 hours urinary albumin excretion (UAE). Of the 8,592 subjects, 1,106 subjects had a high-normal UAE (15-30 mg albumin/day) and 932 had micro-albuminuria (30-300 mg albumin/day).
In principle, subjects from the PREVEND-screening with high-normal UAE or micro-albuminuria were eligible for inclusion in the PREVEND-IT-trial. Further formal inclusion criteria of the PREVEND-IT-trial were persistent albuminuria (once a urinary albumin concentration > 10 mg/l in the early morning spot urine and at least one measurement of 15-300 mg/24 hours in two 24-hours urine samples), a blood pressure < 160/100 mmHg, the absence of anti-hypertensive and lipid lowering medication and a total cholesterol < 8.0 mmol/l, or < 5.0 mmol/l in case of previous myocardial infarction. A total of 864 subjects fulfilled all formal inclusion criteria for PREVEND-IT and were willing to participate in the trial. These subjects were randomized to fosinopril 20 mg or matching placebo and to pravastatin 40 mg or matching placebo.
The primary endpoint of PREVEND-IT was incidence of cardiovascular events; defined as cardiovascular mortality, non-fatal myocardial infarction or myocardial ischemia, heart failure, peripheral vascular disease or cerebrovascular attack.
During follow-up (46±7 months), the primary endpoint occurred in 45 (5.2%) subjects, of which 17 events were in the fosinopril group (n=431) and 28 in the placebo group (n=433). Patients treated with fosinopril had a 40% lower incidence of the primary endpoint than patients in the placebo group (3.9% versus 6.5%, respectively; p= 0.098). Pravastatin resulted in a 13% lower incidence of the primary endpoint compared to placebo (4.8% versus 5.6%, respectively; p=0.649).

Design

Cost-effectiveness of screening for albuminuria was estimated in the baseline analysis and sensitivity analysis (in particular, stochastic- and subgroup analysis). In all calculations, fosinopril treatment subsequent to detection in the screening was assumed, as this study drug showed a relevant (although not statistically significant at the conventional cut-off) effect on the incidence of cardiovascular events. For this purpose, subjects with fosinopril (n=431) were compared with those 433 subjects receiving the fosinopril placebo (in the two by two factorial design this means that half of the subjects with fosinopril and half of those with placebo also got pravastatin). This approach optimised the number of patients to be included for our analysis. In sensitivity analysis, we analysed cost-effectiveness based on that half of the study population in the factorial design, not receiving pravastatin (215 subjects having fosinopril and placebo versus 216 subjects on double placebo).
The study adopted the Dutch health-care perspective and focused on the costs of hospital resource use for CVD-events: hospitalisations, diagnostics and therapeutic procedures. Additionally, the costs for the screening procedure and the drug costs of fosinopril were estimated. Patient-level data on resource use were collected over the full period of study follow-up. All costs were expressed in 2002 €'s.

Costing

Hospital costs
Costs associated with diagnostic and therapeutic procedures for the cardiovascular events of the primary endpoint were derived by multiplying resource use with unit costs taken from the Dutch Tariff Book 2002 [16]. Daily inpatient costs on a regular ward were €199 in a general hospital and €279 in an academic hospital and €889 for ICU, according to the Dutch reference prices for pharmacoeconomic evaluation [17-18]. These costs included specialist, residence and nursing fees. Costs for laundry, nutrition, accommodation and cleaning, overhead and equipment were also included. Medication costs – other than the study drugs - during hospitalisation were not included. Furthermore, the out-patient-visit costs were taken into account at €40 in a general hospital and €70 in an academic hospital [17]. Obviously, every subject with an event had different total hospital costs, depending on the individually consumed diagnostics and therapeutic procedures, the length of hospital stay and the number of visits to the out-patient clinic.

Drug costs
The costs of fosinopril were based on the actual consumption during the study follow-up. The costs for the general practitioner (€18/visit) and pharmacist's fee (€6/prescription per 3 months) related to the drug(s) were also taken into account (no additional visits to the GP were assumed for adverse effects of fosinopril). The costs of medication were obtained from the Dutch Pharmacotherapeutic Guidelines[19].

Screening costs – Screening costs were estimated from the observational PREVEND study. The costs for the pre-screening program, for 85.421 persons initially approached, amounted to €62,700 for apparatus, €76,800 for administration, €61,800 for laboratory materials and €81,400 for personnel. The costs for the screening program were €73,600 for apparatus, €9,100 for administration, €90,000 for laboratory materials, and €328,200 for personnel. For personnel costs, those related to researchers (epidemiologists and statisticians) were excluded, as these would not be part of a routine screening program assumed here. All together the costs for the pre-screening and screening program amounted to €282,700 and €500,900, respectively, adding to €783,600. The screening costs to find one person with micro-albuminuria or high-normal UAE was subsequently estimated at €385, based on 2,038 persons with such characteristics. In subgroup analysis, limitation of treatment to those with a UAE 30-300 mg/day (n=319) or UAE 50-300 mg/day (n=169) was investigated with corresponding higher costs to find one such person (€841 and €1,238, respectively). Screening costs are summarized in Table 1.

Table 1. *Costs of screening in €'s (price level: 2003)*

Total prescreening costs (40,856 subjects)	282,727
Total screening costs (8,592 subjects))	500,909
UAE 15-300 mg/day (2,038 subjects)	385*
UAE 30-300 mg/day (932 subjects)	841*
UAE 50-300 mg/day (633 subjects)	1,238*

* screening costs to find one micro-albuminuric person

Cost-effectiveness Analysis
Cost-effectiveness was expressed in net costs per life-year gained (LYG). In the baseline analysis, net costs result from investment costs in the screening and the costs for fosinopril treatment minus benefits of averted costs related to averted events; i.e. screen & treat is compared to no screening or "doing nothing". Life-years gained were based on losses in remaining life expectancies of subjects with events in both groups (fosinopril and placebo). Loss in remaining life expectancy after a cardiovascular event was estimated using the Dutch adaption of the Framingham study[2] and standard Dutch life-tables (data for 1998 – 2002 of the Central Bureau of Statistics) [20]. Table 2 lists these assumptions (for ages in between those presented interpolation was used). Monetary amounts and life-years gained were discounted at 4%, according to the Dutch guidelines for Pharmaco-economic research [20].

Table 2. *Remaining life expectancy for the general population and for those subjects with a cardiovascular event (CVE) at various Ages.*

Age	General*	After CVE†
Male		
50	27.8	15.9
60	19.3	12.3
70	12.1	8.8
80	6.8	5.3
Female		
50	32.4	20.3
60	23.5	16.1
70	15.4	11.0
80	8.7	7.0

* Dutch Life Tables (the Netherlands Central Bureau of Statistics)
† Framingham life tables adapted to the Dutch population2

Statistical analysis

The bootstrap method (1000 replications) was used to derive 95% confidence intervals for net costs per LYG (cost-effectiveness ratio; CER) [22-23]. In particular, the parametric bootstrap was used, assuming a bivariate normal distribution for mean net costs and mean effect (LYG) [24-25]. To describe the uncertainty in the estimates of the CER, we constructed cost-effectiveness acceptability curves [26]. These curves show probabilities that the intervention of screening and treatment is acceptable given a specific threshold above which the CER is considered unfavorable and below which it is considered favorable. In cost-effectiveness acceptability analysis, we report the median CER and the percentage corresponding to €20,000 per LYG, as this figure is the only published threshold for the Netherlands up to now [27]. We do however note that this threshold is not undisputed and its use should be interpreted with cautiousness.
Sensitivity analysis – Further sensitivity analysis was particularly directed at performance in different subgroups. A number of subgroup analyses have been carried out in order to explore the variation of the results and the potentials for targeted implementation.

Results

The primary endpoint in the PREVEND-IT trial occurred 17 times in the fosinopril group and 28 in the placebo group.

Costs
The costs of cardiovascular events were calculated from the clinical trial at €206 and €148 per subject, in the fosinopril and placebo groups, respectively (Table 3). Per-person costs in the fosinopril group were slightly higher than in the placebo group, primarily because patients (persons with events) in the fosinopril group more often underwent coronary artery bypass grafting (CABG) compared to the placebo group.
Above costs were applied to the screen & treat and the no screening strategies, respectively (Table 3). Adding estimated intervention costs at €1306 for fosinopril treatment (inclusive GP's - and pharmacist's shares) and screening costs at €385, resulted in estimated mean costs of €1888 (1815 if discounted) per person in the screening program. Obviously, no further costs for screening nor for treatment were considered for the no screening option, and resulting total costs were €147 (144 if discounted) per person (Table 3). The difference in discounted costs between screen & treat versus no screening was thus estimated at €1,671 (Table 3).

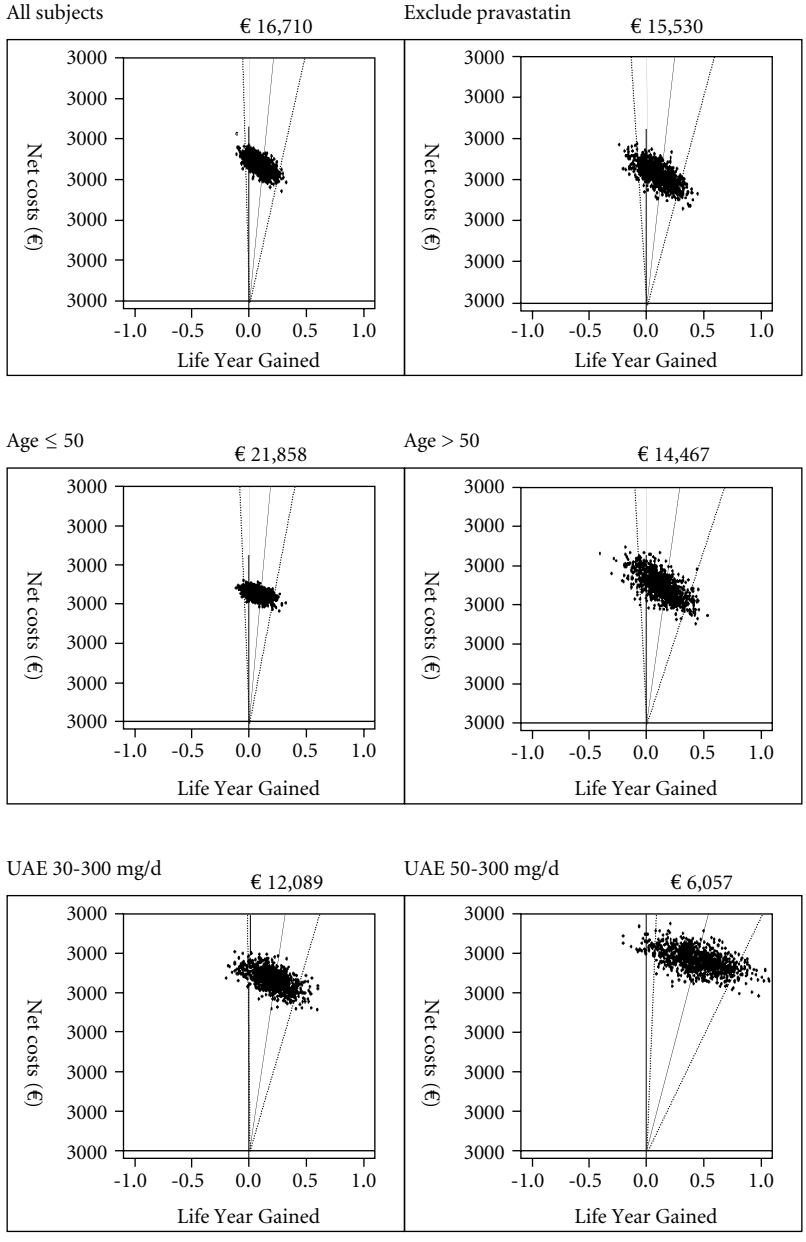
Table 3. *Estimated mean costs in €'s (price level: 2003) per person for various categories in two strategies: screening and treating albuminuric subjects with fosinopril versus no screening and the respective differences.*

	Screen & treat	No screening	Difference
Cardiovascular events	**206**	**148**	**58**
• Procedures	113	68	45
• Hospital contacts	93	80	**13**
Intervention	**1,296**	**0**	**1,296**
• Fosinopril	1,001	0	1,001
• GP and pharmacist	295	0	295
• Screening	385*	0	385
Total Costs			
• Undiscounted	1,888	147	1,741
• Discounted	1,815	144	1,671

* screening costs to find one micro-albuminuric person in the baseline analysis

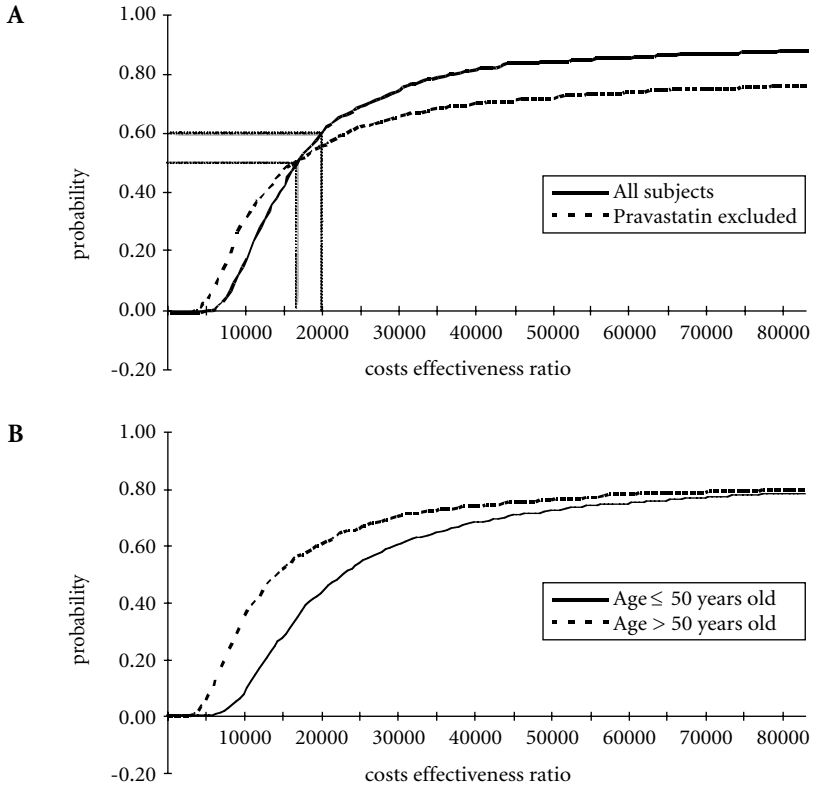
Baseline Analysis
The higher event rate in the placebo compared to the fosinopril group (6.5% versus 3.9%) translated into an estimated mean number of life-years lost at 0.28 per person not using fosinopril versus 0.18 in the fosinopril group. These figures were applied to the no screening and screening options, respectively. Ergo, screening was estimated to gain 0.10 life years per person; i.e. approximately one month.

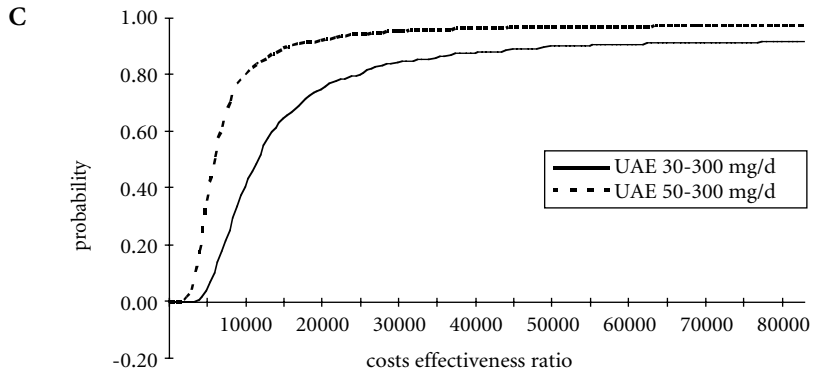
Figure 1 *Cost-effectiveness of screening for albuminuria and subsequent fosinopril treatment versus no screening in the Netherlands, in the baseline and sensitivity analysis. Scatter plots present 1000 replicates per analysis using the bootstrap method, additionally empirical 95%-confidence limits (dotted lines) and estimated means (solid lines and actual figures given) are shown.*



In the baseline analysis, estimated cost-effectiveness was €16,710 per LYG (=€1,671/0.10). Figure 1 shows the corresponding scatter plot of the 1000 bootstrap replications of net costs and effects in the cost-effectiveness plane, the estimated mean and the 95%-confidence interval. Results are spread over the first and fourth quadrant of the cost-effectiveness plane. The estimated mean is below the Dutch threshold of €20,000 per LYG.
Additionally, we determined the probability that the CER is above or below various thresholds for maximum willingness to pay for gaining a life-year (Figure 2). For 50% of the bootstrap replicates in the baseline analysis estimated cost-effectiveness is below €15,690 per LYG (this median is indicated in Figure 2). For a maximum acceptable cost-effectiveness ratio €20,000, the screen & treat option is acceptable in 61% of cases (*see* Figure 2 and Table 4).

Figure 2 *Cost-effectiveness acceptability curves for screening for albuminuria and subsequent fosinopril treatment versus no screening in the Netherlands, in the baseline and sensitivity analysis.* ***A****: all subjects with UAE 15-300 mg/day;* ***B****: subgroups by age (based on median age in PREVEND-IT at 50 years);* ***C****: subgroups by UAE (30 mg/day and 50 mg/day are commonly used alternative cut-off points). Any curve represents the probability (y-axis) that screen & treat is acceptable over a range of cost-effectiveness thresholds of decision makers' willingness to pay (x-axis).*





Sensitivity analysis

Figures 1 and 2 and Table 4 also show the results of the sensitivity analysis. Firstly, restricting our analysis to those subjects not receiving pravastatin did not change our findings. However, the estimated mean cost-effectiveness ratio was lower for those older than 50 years than for subjects of 50 years or younger (€14,470 and €21,860 per LYG, respectively). Median cost-effectiveness estimates were similar (Figure 2). Finally, limiting treatment to only those micro-albuminuric subjects with a relatively high UAE than in the baseline lowered cost-effectiveness considerably to €12,100 for those with a UAE above 30 mg/day, or even down to € 6,100 per LYG for those excreting more than 50 mg albumin per day (Figure 1). In the latter case, the probability of being cost-effective (below € 20,000 per LYG) becomes more than 90% (Figure 2).

Table 4. *Median cost-effectiveness from the cost-effectiveness acceptability curve (Figure 2) and probability of acceptable cost-effectiveness given a threshold of €20,000 per life-year gained*

	Median	**Probability**
Baseline	€ 15,670	0.61
Pravastatin excluded	€ 15,530	0.56
Age > 50	€ 14,470	0.61
Age <51	€ 21,860	0.43
UAE 30-300 mg/ day	€ 12,100	0.75
UAE 50-300 mg/ day	€ 6,100	0.92

Discussion

This study shows the cost-effectiveness of fosinopril in primary prevention of cardiovascular events in albuminuric subjects from the Dutch health-care perspective. We estimated the mean cost-effectiveness ratio of screening and subsequent active fosinopril treatment at €16,710 per LYG in the baseline analysis. With a maximum acceptable cost-effectiveness of €20,000 per LYG – as has been recently published - our point estimate would be considered cost-effective and probabilistic analysis indicates an estimated

probability of 61% for the screen & treat strategy to be cost-effective. Although the latter percentage does not prove statistically significant favorable cost-effectiveness, one may conclude from our study that screening for albuminuria and subsequent fosinopril treatment is worth to consider from a Pharmaco-economic perspective, based on the mean and on the fact that the majority of cases indicated by the probabilistic sensitivity analysis show a favorable ratio.

We used the factorial design in our economic analysis in such a way that results would be based on maximum numbers of patients included in the trial. This implied that in comparing groups with and without fosinopril, half of both groups were on pravastatin additionally. In sensitivity analysis, we investigated the exclusion of those subjects and found similar results, justifying our use of the factorial design for the economic analysis. Further, sensitivity analysis revealed that cost-effectiveness varied by subgroup. In particular, for subjects older than 50 years a relatively more favorable cost-effectiveness was estimated. Also, limitation to only those subjects with a UAE above 30 – or even above 50 mg/day – improved cost-effectiveness further. Whether this warrants limitation of any considered screen & treat strategy to those subgroups requires additional studies, as these specific subgroups are represented only by relatively small numbers in our trial.

Our study did not explicitly assume specificity and sensitivity of the testing sequence in the screening (one UAC- and two 24-hours UAE-measurements). Testing performance is implicitly incorporated in our analysis. Pre-screening by measuring UAC in a spot morning urine sample is satisfactorily predictive of the UAE (specificity 85%). Obviously, some subjects with elevated albumin levels will be missed (estimated sensitivity also at 85%), but this pre-screening keeps the burden and costs for a population screening as low as possible [28].

Only one study that is comparable to ours could be detected in the literature. Boulware *et al* investigated initial dipstick screening for proteinuria in the general population, with follow-up tests to confirm proteinuria and to start ACE-inhibitor treatment. Obviously, screening for proteinuria yields lower numbers of subjects than screening for albuminuria does in our approach, primarily explaining the much higher cost-effectiveness ratios found by Boulware *et al* for screening the general population, ranging from US$53,370 to 282,800 per quality-adjusted life-year (QALY) gained. Additionally, further differences between both approaches exist: (1) different health-care systems; (2) different implementations (GP-based versus systematic postal) and (3) in- or exclusion of cardiovascular risks. We do note that – given the favorable cost-effectiveness of ACE-inhibitor therapy for proteinuria [10,29] – inclusion of fosinopril treatment for screened overt proteinuric subjects, instead of only those with an UAE of 15-300 mg/day, would improve cost-effectiveness in our study.

Still, cost-effectiveness of ACE-inhibitor therapy in non-proteinuric populations has been studied previously. Bjorholt *et al* did a sub-study of the HOPE-trial on the Swedish participants to estimate the cost-effectiveness of ramipril treatment for patients with vascular disease or diabetes [7]. The principal finding indicated net costs per LYG at €1,940-5300. Note that this estimate includes treatment only, no (costs of) screening was considered. Based on our data, we could estimate cost-effectiveness of fosinopril treatment of albuminuric subjects at €12,780 in the baseline analysis.

Also, cost-effectiveness analysis of ACE-inhibitor therapy as first line antihypertensive compared to conventional therapy of beta-blockers or diuretics has been studied previously [4]. Nordmann *et al* reported estimated cost-effectiveness ranging from US$200,000

to 700,000/QALY. Obviously, this range presents a cost-effectiveness that can never be considered acceptable given any threshold defined so far internationally.
The major 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, our study was based registered on events in patients as they occurred during the follow-up of the PREVEND-IT trial, minimizing the number of assumptions required to perform the whole analysis. Still, the inherent limitation of this is that our study lacks the patient data beyond the endpoints, such as nursing home care for stroke, rehabilitation after acute events and potential re-hospitalizations, with corresponding costs. It may thus be argued that the calculation of cost-effectiveness may – in reality – be even more favorable. However, we should also note that – given the limited follow-up in the PREVEND-IT trial - lifetime health gains had to be modeled using Dutch data on remaining life expectancy and Framingham life tables.
Further work on our approach should involve the combination of cardiovascular events and progression of renal disease. For the purpose of this combination a Markov model could be developed with stages corresponding to albumin levels, transition probabilities derived from various trials and cardiovascular risks factored into the different stages. Such models have been developed for diabetes patients focusing on renal disease, however still lack the formal inclusion of cardiovascular risks [30-31].
What may be the implications of our study for health policy? Our current study clearly shows that major potentials for favorable cost-effectiveness exist for a screening program for albuminuria in the general population. The overall baseline cost-effectiveness estimated at €16,710 per LYG is below the only defined threshold for cost-effectiveness in the Netherlands at €20,000 per LYG [27]. Cost-effectiveness may be further improved if screening is limited to predefined subgroups, for example, by age or albumin level. Further research is needed to confirm our findings in other settings and using additional trials on the issue.

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