BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2008.03097.x

Baseline albuminuria predicts the efficacy of blood pressure-lowering drugs in preventing cardiovascular events

Cornelis Boersma, Maarten J. Postma, Sipke T. Visser, Jarir Atthobari, Paul E. de Jong,[1] Lolkje T. W. de Jong-van den Berg & Ron T. Gansevoort[1] on behalf of the PREVEND Study Group

Groningen Research Institute of Pharmacy (GRIP), University of Groningen and [1]Department of Internal Medicine, Division of Nephrology, University Medical Centre Groningen (UMCG), Groningen, the Netherlands

Correspondence
Cornelis Boersma Msc (Pharm), Department of Social Pharmacy, Pharmacoepidemiology & Pharmacotherapy, University of Groningen, Antonius Deusinglaan 1, 9713 AV, Groningen, the Netherlands.
Tel: + 31 50 363 8204
Fax: + 31 50 363 2772
E-mail: c.boersma@rug.nl

Keywords
albuminuria, blood pressure, cardiovascular diseases, prevention

Received
26 October 2007

Accepted
3 December 2007

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Albuminuria has been proven to be associated with cardiovascular morbidity and mortality.
- Such an association has been found not only in subjects with diabetes and hypertension, but also in the general population.
- It could therefore be expected that especially subjects with higher albuminuria levels may benefit from blood pressure-lowering agents to improve their cardiovascular outcome.

WHAT THIS STUDY ADDS

- This study indicates that the efficacy of blood pressure-lowering agents to prevent cardiovascular events is dependent of the level of albuminuria before start of such treatment.
- The higher baseline albuminuria, the better the relative and absolute risk reduction for cardiovascular events with blood pressure-lowering drugs.
- The data also suggest a possible better cardiovascular protective effect of renin–angiotensin intervening agents compared with other blood pressure-lowering agents.

AIMS

Albuminuria has been proven to be associated with cardiovascular (CV) events in specific patient populations, but also in the general population. This study aimed to investigate whether the efficacy of blood pressure-lowering agents in preventing CV events depends on baseline urinary albumin excretion (UAE) and, if so, whether this holds true for blood pressure-lowering agents in general, or is limited to agents that interfere in the renin–angiotensin system.

METHODS

Data were used from a community-based cohort study and pharmacy dispensing records. Included were subjects with hypertension (systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg), no cardiovascular disease history, and no previous use of blood pressure-lowering agents.

RESULTS

During study follow-up (7.1 ± 1.6 years), 122 CV events were observed in 1185 subjects included. Start of blood pressure-lowering agents *vs.* non-use was associated with a difference in absolute CV event risk of 0.7%, 6% and 12.6% for all subjects, those with UAE ≥ 15 mg day^{-1} and ≥30 mg day^{-1}, respectively. Cox regression analysis showed that the relative risk for CV events after start of blood pressure-lowering agents was significantly dependent ($P < 0.05$) on baseline UAE; with hazard ratios of 0.87 [95% confidence interval (CI) 0.48, 1.60, P = NS], 0.58 (95% CI 0.36, 0.94, $P < 0.05$) and 0.37 (95% CI 0.20, 0.68, $P < 0.05$), for subjects with UAE < 15, ≥15 and ≥30 mg day^{-1}, respectively. Results adjusted for covariates were essentially similar. The use of angiotensin converting enzyme inhibitor/angiotensin-II receptor blocker (ACEi/ARB) treatment tended to be associated with a more favourable CV prognosis when compared with non-ACEi/ARB treatment (difference $P = 0.06$).

CONCLUSIONS

Our results suggest that the efficacy of blood pressure-lowering agents to prevent CV events is dependent on baseline albuminuria. The higher baseline albuminuria, the more absolute as well as relative risk reduction can be achieved. Our data suggest that this may especially be true for ACEi/ARBs. We caution that this is an observational study, and that these conclusions should therefore be regarded as hypothesis generating, rather than hypothesis testing.

Introduction

Blood pressure-lowering agents are prescribed to lower the cardiovascular (CV) event rate. Ideally, these agents should be prescribed preferentially to those subjects at increased CV risk [1–4]. Risk prediction models have been developed to estimate the CV risk of an individual, such as the Framingham Risk Score and the SCORE Risk Model. These prediction models take into account various risk factors for CV disease, as well as signs of atherosclerosis-related end organ damage. In general, these risk prediction models do not contain urinary albumin excretion (UAE) [5].

In various cross-sectional studies it has been found that albuminuria is associated with CV risk factors such as age, gender, blood pressure, cholesterol, glucose, body mass index (BMI) and smoking [6–13]. Prospective studies have shown that higher albuminuria levels predict worse CV outcome, even independent of the above-mentioned risk factors. Such observations were done not only in subjects with diabetes and hypertension, but also in the general population [14–20]. It is therefore tempting to hypothesize that especially subjects with higher albuminuria levels may benefit from blood pressure-lowering agents to improve their CV outcome [21].

We recently completed the PREVEND IT Study, a prospective study in which subjects were randomized to placebo or the angiotensin converting enzyme inhibitor (ACEi) fosinopril [22]. To be eligible subjects had to have albuminuria >15 mg day^{-1} and normal blood pressure and cholesterol, as defined by prevailing guidelines for general practitioners at the start of the study in 1998. In these subjects, apparently at low CV risk, the ACEi lowered the incidence of CV events. In subjects with higher baseline albuminuria the absolute risk reduction with ACE inhibition was greater. Of more interest was the observation that also the relative risk (RR) reduction with the ACEi was found to be dependent on baseline albuminuria: the higher baseline albuminuria, the greater the RR reduction [22]. Since the PREVEND IT study is placebo controlled, it is impossible to ascertain whether the reduction in CV event rate is due to an ACEi-specific effect, or merely due to the blood pressure-lowering effect of this drug class. Furthermore, participants in the PREVEND IT study were only included with persistent albuminuria and therefore it was not formally tested whether the RR reduction with active therapy was significantly greater in subjects with high *vs.* low albuminuria levels.

To provide answers to these issues we decided to analyse data obtained in a community-based prospective cohort study, investigating whether the efficacy of blood pressure-lowering agents to lower the CV event rate is dependent on baseline albuminuria. Second, if such an effect is to be found, to study whether this effect is specific for agents that interfere with the renin–angiotensin system [ACE/angiotensin-II receptor blocker (ARBs)] or can also be observed with other classes of blood pressure-lowering drugs.

Methods

Study design and population

This analysis uses data of the PREVEND study, a prospective observational cohort study designed to investigate the impact of albuminuria on the development of renal and CV diseases in the general population. The design of the PREVEND study has been described in detail elsewhere [13, 23], and can be found on http://www.PREVEND.org. In summary, participating subjects were selected in 1997 from 40 856 individuals from the general population. A cohort aged 28–75 years, enriched for higher levels of albuminuria, was drawn from these individuals. A total of 8592 subjects gave written informed consent and were included in the baseline screening that took place between 1997 and 1998. The PREVEND study has been approved by the local medical ethics committee and was conducted in accordance with the guidelines of the Declaration of Helsinki.

For the present analyses those individuals were included who had detailed pharmacy records on drug use available, who were at the date of the baseline screening hypertensive [defined as systolic blood pressure (SBP) $\geq$140 and/or diastolic blood pressure (DBP) $\geq$90 mmHg [4]], without a CV disease history and not using blood pressure-lowering agents (Figure 1). For the remaining subjects, it was evaluated whether they did or did not start using blood pressure-lowering drugs during study follow-up ('non-users' and 'starters', respectively) (Figure 1). In both groups the incidence of CV events was studied during follow-up. Of note, subjects that started using blood pressure-lowering drugs after a CV event took place were classified as 'non-users', since these subjects had not been exposed to blood pressure-lowering drugs before the event occurred.

Measurements and definitions

The baseline screening procedure consisted of a physical examination and a questionnaire on demographics and medical history. During the physical examination, weight, height and blood pressure were measured. BMI was calculated as weight (kg) divided by the square of height (m^2). SBP and DBP were measured on two occasions in supine position on the right arm every minute for 10 min, with an automatic Dinamap XL model 9300 series monitor (Johnson-Johnson Medical Inc., Tampa, FL, USA). Blood pressure was calculated as the mean of the last two measurements at both occasions. Mean arterial pressure (MAP) was assessed as one-third of the SBP and two-thirds of the DBP. Additionally, fasting blood was drawn for the determination of total cholesterol, glucose and serum creatinine levels. Furthermore, for the measurement of albuminuria

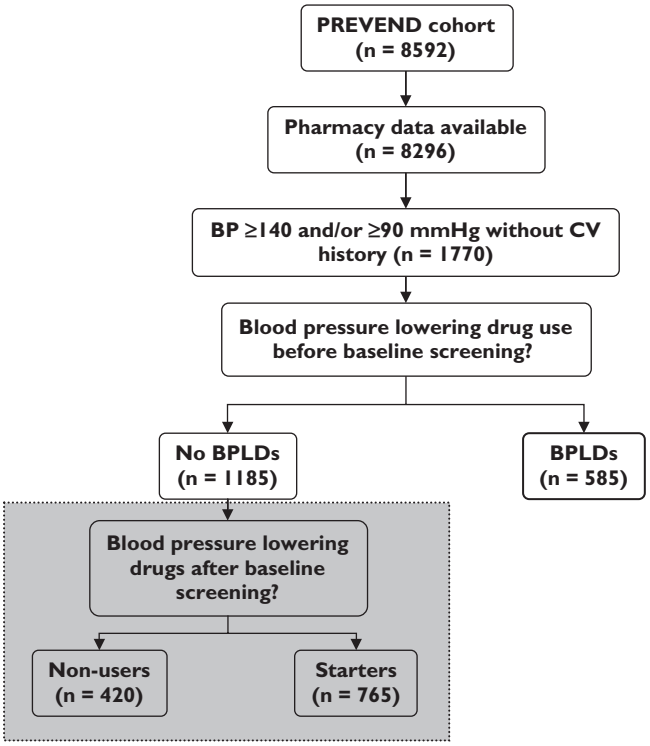

Figure 1

Study-population selection. BP, Blood pressure; CV, cardiovascular disease; BPLD, blood pressure-lowering drugs

two 24-h urine samples were collected after thorough oral and written instructions on how to perform urine collection.

Plasma total cholesterol, plasma glucose and serum creatinine were determined by Kodak Ectachem dry chemistry (Eastman Kodak, Rochester, NY, USA), an automatic enzymatic method. Serum creatinine was measured by photometric determination with the Jaffe method without deproteinization (Merck kgaA, Darmstadt, Germany). Glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) formula. Urine albumin concentration (UAC) was determined by nephelometry (Dade Behring Diagnostic, Marburg, Germany). Albuminuria is given as the mean UAE in the two 24-h urine collections (UAE in mg day^{-1}).

Information on drug use

Data on drug use was obtained from the Inter-Action Data-Base (IADB), which comprises pharmacy-dispensing data of community pharmacists located in the Netherlands [24]. These pharmacies provide the IADB database a complete listing of patient-specific dispensed drugs [25]. The pharmacy data contain information about patient-specific drugs dispensed, e.g. the name of a drug, the Anatomical Therapeutical Chemical (ATC) classification, the date of prescription, the number of days for which a drug was prescribed, and the number of dispensed defined daily doses (DDDs). DDDs for blood pressure-lowering drugs have been defined by the World Health Organization, with units intended to represent dosages with approximately similar efficacy. For example, enalapril 20 mg od has been defined in 1 DDD, as is amlodipine 10 mg od and metoprolol SR 100 mg od [26]. Correcting for dispensed DDDs in regression analysis allows among others for comparison of efficacy between drugs within a class and between classes.

Blood pressure-lowering drug use was defined as at least one prescription of antihypertensives (ATC = 'C02'), diuretics (ATC = 'C03'), β-blockers (ATC = 'C07'), calcium-channel blockers (ATC = 'C08') or ACEi/ARBs (ATC = 'C09'). Information on drug use was available from at least half a year before the baseline screening until date of death or end of follow-up.

Outcome definitions

The primary outcome variable 'cardiovascular events' was defined as a composite end-point consisting of the incidence of CV morbidity or mortality during follow-up. Follow-up time was defined as the period from the date of urine collection of the participant to the date of first CV event, last contact (census) date or 31 December 2005. In case a person had moved to an unknown destination, the date on which the person was removed from the municipal registry was used as census date. Data on CV morbidity was obtained from PRISMANT, the Dutch national registry of hospital discharge diagnoses [27]. Causes of death were obtained from the Dutch Central Bureau of Statistics [28]. All data were coded according to the International Classification of Diseases (ICD), 9th revision and the classification of interventions. For this study, CV events were defined according the Major Adverse Cardiovascular Events (MACE) criteria as acute myocardial infarction (ICD-code 410), acute and subacute ischaemic heart disease (ICD-code 411), subarachnoid haemorrhage (ICD-code 430), intracerebral haemorrhage (ICD-code 431), other intracranial haemorrhage (ICD-code 432), occlusion or stenosis of the precerebral (ICD-code 433) or cerebral arteries (ICD-code 434), coronary artery bypass grafting or percutaneous transluminal angioplasty, and other vascular interventions such as percutaneous transluminal angioplasty or bypass grafting of aorta peripheral vessels.

Statistical analyses

Baseline characteristics are reported as mean and SD for continuous variables and as a percentage for categorical variables. Differences in characteristics between starters on blood pressure-lowering drugs and non-users were tested for continuous variables by Student's *t*-test, for categorical variables by a χ^2 test, and for variables with skewed distribution by a Mann–Whitney test.

In our observational analysis, the effect was compared of starting blood pressure-lowering drugs *vs.* no use concerning the incidence of the composite end-point of CV morbidity and mortality. A crude RR was calculated for subjects who started blood pressure-lowering drugs during follow-up for the incidence of the composite end-point using a univariate Cox regression model and with subjects not using blood pressure-lowering drugs as reference category. Multivariate Cox regression models were built to estimate a RR adjusted for baseline characteristics (age, sex, BMI, smoking, MAP, cholesterol, glucose, serum creatinine, eGFR, albuminuria, start of lipid-lowering drugs and start of blood glucose-lowering drugs). Furthermore, propensity scores were applied in the regression models (next to other covariates) to account for differences in characteristics between the index group ('starters') and the reference group ('non-users') [29, 30]. The propensity score for an individual can be used to reduce bias by indication in observational studies by means of weighing covariates associated with start of drugs. In our analyses, the estimated propensity score for blood pressure-lowering drug use was obtained from the fit of a logistic regression model including the following variables: age, sex, BMI, smoking, MAP, cholesterol, glucose, serum creatinine, eGFR, albuminuria, start of lipid-lowering drugs and start of blood glucose-lowering drugs.

This study aimed at investigating the effect of blood pressure-lowering drugs in preventing CV events in relation to baseline albuminuria level. Cox proportional hazards regression analysis was used to assess such a possible interaction, crude as well as adjusted for covariates. For this purpose an interaction term was included, 'start of blood pressure-lowering agent' times 'albuminuria level'. In case the interaction term contributed significantly to the model, it was decided that the efficacy of blood pressure-lowering agents depends on baseline albuminuria and further analyses were to follow. In the first analysis, the threshold defining elevated albuminuria was set at a UAE level of 15 mg day^{-1}, consistent with previous work [22]. An additional analysis was performed in subjects with albuminuria $\geq$30 mg day^{-1}. Further analyses were conducted investigating first the effect of the level of drug exposure, and second the efficacy of ACEi/ARBs *vs.* non-ACEi/ARB agents in preventing CV events. For the analysis with respect to blood pressure-lowering drug exposure, patient-specific total number of prescribed DDDs was calculated and divided by total days of study follow-up from date of first screening until the date of a first event, or until the census date, or until 31 December 2005. Exposure is expressed as average number of DDDs per day (DDDs day^{-1}).

All analyses were conducted using the statistical package SPSS 14.0 (SPSS Inc., Chicago, IL, USA). A *P*-value < 0.05 (two-tailed) was considered to be statistically significant.

Results

Baseline characteristics

Of the PREVEND cohort consisting of 8592 subjects, complete pharmacy data were available for 8296 participants (Figure 1). Subjects with normal blood pressure (<140/90 mmHg) and with a CV disease history were excluded ($n = 6526$). Out of the 1770 subjects with elevated blood pressure, 585 participants received at least one prescription of a blood pressure-lowering drug during the half-year period before the baseline screening and were therefore excluded. Of the remaining 1185 subjects followed in this observational study, 765 started and 420 did not start using blood pressure-lowering drugs during follow-up (Figure 1).

The baseline characteristics of these latter two groups are reported in Table 1. For this table subjects were divided into different groups based on albuminuria level (UAE) and whether or not they started use of blood pressure-lowering drugs after the baseline screening. Those who started use of blood pressure-lowering drugs had significantly higher age and blood pressure, and more frequently started use of lipid-lowering and blood glucose-lowering drugs compared with the 'non-user' group, both in the normal (UAE $<$ 15 mg day^{-1}) and the elevated (UAE $\geq$15 mg day^{-1}) albuminuria groups. Furthermore, in subjects with normal albuminuria the 'starter' group had significantly higher glucose levels, and in subjects with elevated albuminuria 'starters' had a lower eGFR.

Follow-up data

Total follow-up for this observational study until occurrence of a CV disease event, census date or until the end of the study period amounted to 8378 person-years, with a mean follow-up of 7.1 years (SD 1.6) per subject included. Table 2 shows the number of (first) CV events that occurred during follow-up, both with respect to the composite end-point and as the individual components. As the current study was designed as a 'time-to-first-event' study, only first events are shown. The composite end-point of CV morbidity and mortality occurred in 122 (11.2%) subjects, with 42 (6.9%) in the normal albuminuria group ($n = 611$) and 80 (13.9%) in the elevated albuminuria group ($n = 574$). These data show that participants with elevated albuminuria have a higher risk of reaching the composite end-point compared with subjects without elevated albuminuria, with a crude RR of 2.03 [95% confidence interval (CI) 1.42, 2.90].

Figure 2 shows the results on the difference in absolute risk for the composite end-point for 'starters' on *vs.* 'non-users' of blood pressure-lowering drugs. In the overall population, start of blood pressure-lowering drugs was associated with a difference in absolute risk for CV events of 0.7% *vs.* no use, which was not statistically significant ($P = 0.80$). For the subgroup of subjects with normoalbuminuria, comparable results were found with a difference

Table 1

Baseline characteristics

	UAE < 15 mg day^{-1} (n = 611)			UAE ≥ 15 mg day^{-1} (n = 574)		
	Non-user (n = 291)	Starter (n = 320)	P-value	Non-user (n = 129)	Starter (n = 445)	P-value
Age, years (SD)	52.9 (12.5)	56.0 (11.3)	0.001*	55.4 (12.4)	58.6 (10.7)	<0.01*
Gender, male, %	56.0	54.7	0.74†	72.1	62.9	0.06†
BMI, kg m^{-2}, (SD)	27.1 (3.9)	27.1 (3.8)	0.93*	28.4 (4.9)	28.5 (4.4)	0.88*
Smoking, %	34.7	38.4	0.34†	42.6	42.9	0.95†
DBP, mmHg (SD)	80.6 (7.5)	83.7 (7.3)	<0.001*	82.4 (7.4)	86.9 (9.4)	<0.001*
SBP, mmHg (SD)	148.1 (8.3)	154.0 (13.1)	<0.001*	151.2 (10.3)	159.5 (15.9)	<0.001*
MAP, mmHg (SD)	103.1 (6.5)	107.2 (7.4)	<0.001*	105.3 (7.1)	111.1 (10.0)	<0.001*
Plasma cholesterol, mmol l^{-1} (SD)	6.0 (1.3)	5.9 (1.3)	0.40*	5.8 (1.3)	6.0 (1.3)	0.28*
Plasma glucose, µmol l^{-1} (SD)	4.9 (1.0)	5.0 (1.0)	<0.05*	5.5 (1.9)	5.5 (1.9)	0.68*
Serum creatinine, µmol l^{-1} (SD)	83.3 (15.2)	83.6 (16.3)	0.77*	86.6 (18.8)	86.9 (18.7)	0.84*
eGFR, ml min^{-1} 1.73 m^{-2} (SD)	80.6 (14.4)	78.7 (14.3)	0.10*	80.3 (14.1)	77.3 (14.7)	<0.05*
Albuminuria, mg day^{-1} (95% CI)	8.5 (3.1, 14.8)	8.9 (0, 15.0)	0.07‡	30.7 (15.0, 763.9)	35.5 (15.1, 2688.9)	0.06‡
Start of lipid lowering drugs, %	11.3	35.0	<0.001†	20.9	48.3	<0.001†
Start of blood glucose-lowering drugs, %	3.1	10.0	<0.001†	6.2	17.1	<0.05†

Continuous variables are presented as mean and standard deviation (SD) and categorical variables as percentage. Urinary albumin excretion is given as geometric mean and 95% CI. BMI, Body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; MAP, mean arterial blood pressure; eGFR, estimated glomerular filtration rate. *t-test. †χ^2 test. ‡Mann–Whitney test.

Table 2

Incidence of the composite cardiovascular end-point, and individual components in all subjects, stratified according to albuminuria class. Since analyses are time-to-first event based, for participants included only first events during follow-up are presented

	All subjects (n = 1185)	UAE < 15 mg day^{-1} (n = 611)	UAE ≥ 15 mg day^{-1} (n = 574)
Composite end-point (%)	122 (11.2)	42 (6.9)	80 (13.9)
Individual components:			
Cardiovascular death	3	1	2
Nonfatal events			
– Cardiac*	78	29	49
– Cerebrovascular†	31	11	20
– Peripheral disease‡	10	1	9

*Cardiac disease events: myocardial infarction, ischaemic heart disease, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty. †Cerebrovascular disease events: subarachnoid haemorrhage, intracerebral haemorrhage, occlusion and stenosis of precerebral arteries, occlusion of cerebral arteries. ‡Peripheral vascular disease events: aorta peripheral bypass surgery, percutaneous transluminal femoral angioplasty.

in absolute risk of 0.6% (P = 0.87). In contrast, the higher baseline albuminuria, the more pronounced the absolute risk reduction for the composite end-point in 'starters' *vs.* 'non-users' of blood pressure-lowering drugs. In the subgroup of subjects with albuminuria ≥15 mg day^{-1} the absolute risk amounted 18.6% ('non-users') *vs.* 12.6% ('starters'), with a difference in absolute risk of 6.0% (P = 0.11), whereas in the subgroup of subjects with albuminuria ≥30 mg day^{-1} these figures were 24.6% and 12.0%, respectively (absolute difference 12.6%, P < 0.05).

Table 3 shows the unadjusted and adjusted hazard ratios (HRs) for the composite CV end-point of subjects who started use of blood pressure-lowering drugs during follow-up with subjects who did not use such drugs as reference category. For the overall population a statistically nonsignificant difference in the composite end-point was found for subjects starting on blood pressure-lowering drugs compared with non-users (HR = 0.87; 95% CI 0.61, 1.26). After adjustment for baseline characteristics, this difference in risk increased and was statistically significant (HR = 0.54; 95% CI 0.36, 0.83, P < 0.01). Further adjustment also with propensity score left this unchanged (HR = 0.52; 95% CI 0.34, 0.80, P < 0.01).

A possible interaction between blood pressure-lowering drug use and albuminuria on CV outcome was tested in the overall crude, as well as adjusted Cox proportional hazards models. The 'start of blood pressure-lowering agent' times 'albuminuria level' interaction term was significantly associated with the outcome in all

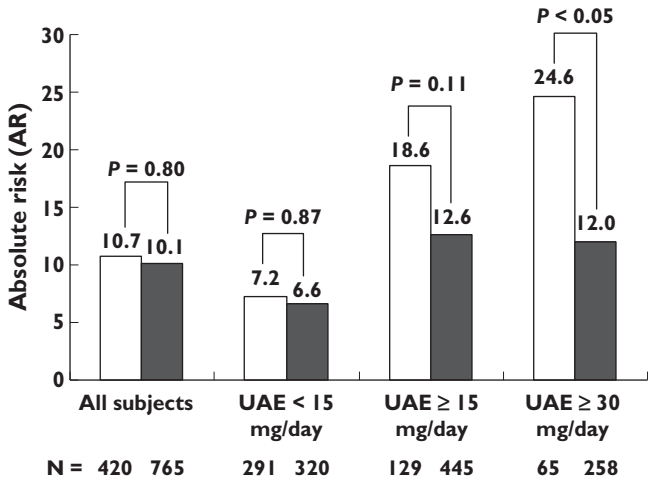

Figure 2

Absolute risk for the incidence of the combined end-point of cardiovascular morbidity and cardiovascular death for subjects who started ('starters', (■)) and did not start ('non-users', (□)) treatment with blood pressure-lowering drugs during follow-up. UAE, Urinary albumin excretion. *N* indicates the number of subjects in each group. Unadjusted *P*-values* calculated using a χ^2 test. **P*-values representing the significance level after follow-up correction are $P = 0.47$, $P = 0.66$, $P < 0.05$ and $P < 0.05$ for all subjects, and those subjects with UAE < 15 mg day^{-1}, UAE ≥ 15 mg day^{-1} and UAE ≥ 30 mg day^{-1}, respectively

models ($P < 0.05$), indicating that the benefit of blood pressure-lowering drugs was greater in subjects with higher albuminuria levels.

Cox proportional hazards regression analyses based on subgroups confirmed that the RR for CV events with blood pressure-lowering drug use depends on baseline albuminuria level with unadjusted HRs for all subjects being 0.87 (95% CI 0.61, 1.26, P = NS), for subjects with UAE < 15 mg day^{-1} 0.87 (95% CI 0.48, 1.60, P = NS), for subjects with UAE = 15 mg day^{-1} 0.58 (95% CI 0.36, 0.94, $P < 0.05$) and for subjects with UAE = 30 mg day^{-1} 0.37 (95% CI 0.20, 0.68, $P < 0.05$). Table 3 shows that the results are essentially similar after adjustment for age, sex, baseline characteristics, start of lipid-lowering and blood glucose-lowering agents and propensity scores. These results are graphically depicted in Figure 3.

Table 4 provides data on only subjects starting blood pressure-lowering drugs during follow-up. It shows that subjects with higher baseline albuminuria had higher exposure to blood pressure-lowering drugs. The role of exposure to such drugs was investigated, showing that high exposure (average number of DDDs day^{-1} ≥ 0.75) was associated with lower chance to reach the composite end-point compared with low exposure (average number of DDDs day^{-1} < 0.75) (Table 3). Since this may influence the results obtained, the RRs to reach the composite end-point denoted in Table 3 are in the final model also adjusted for level of exposure to blood pressure-lowering drugs.

The question whether agents that interfere with the renin–angiotensin system (ACEi/ARB) differ from other blood pressure-lowering drugs in their efficacy in preventing CV events is also addressed in Table 3. It shows that subjects using only ACEi/ARB treatment had a HR of 0.63 to reach the composite end-point compared with those receiving non-ACEi/ARB treatment only. Whereas this difference is not statistically significant in the crude analysis, there is a trend towards statistical significance after adjustment for baseline characteristics, propensity score and level of exposure ($P = 0.06$). As found for the whole group of blood pressuring-lowering drugs, the effect of ACEi/ARB treatment turned out to be significantly dependent on baseline albuminuria ($P < 0.05$ for the interaction term 'start of ACEi/ARB' times 'albuminuria level'). Such an association was not found for non-ACEi/ARB treatment.

Discussion

Besides the finding that blood pressure-lowering agents are effective in ameliorating the CV outcome, our observational data show that in hypertensive subjects without a CV disease history the risk of reaching a CV event during follow-up is dependent on baseline albuminuria. The higher baseline albuminuria in such subjects, the higher the risk for CV disease. As expected, start of treatment with blood pressure-lowering drugs is associated with a decrease in CV risk, with absolute risk reduction being superior in subjects with higher baseline albuminuria and corresponding number needed to treat (NNT) to prevent one CV event of 153 vs. 17 for those subjects with UAE < 15 mg day^{-1} and UAE ≥ mg day^{-1} respectively. For subjects with UAE < 30 mg day^{-1} and UAE ≥ 30 mg day^{-1} NNTs were 111 and 8, respectively. More interesting, however, is our finding that the RR reduction for CV events with blood pressure-lowering agents is also dependent on baseline albuminuria. The higher baseline albuminuria, the better the RR reduction. Furthermore, the CV protective effect of ACEi/ARBs in subjects with higher albuminuria seems to be better than that of other blood pressure-lowering agents. However, possible interindividual variation in responses to different types and doses of blood pressure-lowering agents could have influenced these results. Further research should be directed at blood pressure-lowering efficacy, correcting for these potential differences, before definite conclusions may be drawn.

How do these data compare with the literature? Several epidemiological studies have shown that albuminuria is a valuable risk marker for CV disease in various patient populations, such as diabetics and hypertensives, and even in the general population [14–20]. Numerous randomized controlled trials have shown that blood pressure-lowering agents improve CV outcome [31, 32]. Little is known, however, of a possible interaction between albuminuria and the cardioprotective efficacy of blood pressure-lowering agents. As discussed in the Introduction, the PREVEND-IT study suggested that active treatment *vs.*

Table 3

Effect of the start of blood pressure-lowering drugs

	n	End-point (%)*	Crude HR (95% CI)†	Adjusted HR (95% CI)‡	Adjusted HR (95% CI)§
All subjects					
Non-users	420	45 (10.7)	1.00	1.00	1.00
Starters	765	77 (10.1)	0.87 (0.61, 1.26)	0.54 (0.36, 0.83)	0.52 (0.34, 0.80)
UAE < 15 mg day^{-1}					
Non-users	291	21 (7.2)	1.00	1.00	1.00
Starters	320	21 (6.6)	0.87 (0.48, 1.60)	0.55 (0.28, 1.10)	0.56 (0.28, 1.12)
UAE ≥ 15 mg day^{-1}					
Non-users	129	24 (18.6)	1.00	1.00	1.00
Starters	445	56 (12.6)	0.58 (0.36, 0.94)	0.44 (0.26, 0.75)	0.42 (0.24, 0.72)
UAE ≥ 30 mg day^{-1}					
Non-users	65	16 (24.6)	1.00	1.00	1.00
Starters	258	31 (12.0)	0.37 (0.20, 0.68)	0.33 (0.16, 0.69)	0.31 (0.15, 0.65)
Starters only					
Low exposure < 0.75 DDDs day^{-1}	453	48 (10.6)	1.00	1.00	1.00
High exposure ≥ 0.75 DDDs day^{-1}	312	29 (9.3)	0.87 (0.55, 1.37)	0.72 (0.42, 1.23)¶	0.70 (0.40, 1.20)¶
Starters only					
Non-ACEi/ARB only	219	29 (13.2)	1.00	1.00	1.00
ACEi/ARB only	155	13 (8.3)	0.63 (0.33, 1.22)	0.51 (0.25, 1.01)††	0.51 (0.26, 1.03)††

*Number of persons and percentage with the composite end-point (cardiovascular morbidity or mortality). †Crude relative risk without any adjustment for baseline characteristics. ‡Adjusted for age, sex, body mass index (BMI), smoking, mean arterial pressure (MAP), cholesterol, glucose, serum creatinine, estimated glomerular filtration rate (e-GFR), urinary albumin excretion (UAE), start of lipid-lowering drugs and start of blood glucose-lowering drugs. §Adjusted for all previously mentioned variables including propensity scores. ¶Additional adjustment for exposure to type of blood pressure-lowering drug (categorized variable: non-ACEi/ARB only, ACEi/ARB only or both types). ††Additional adjustment level of exposure to blood pressure-lowering drugs (average number of DDDs per day).

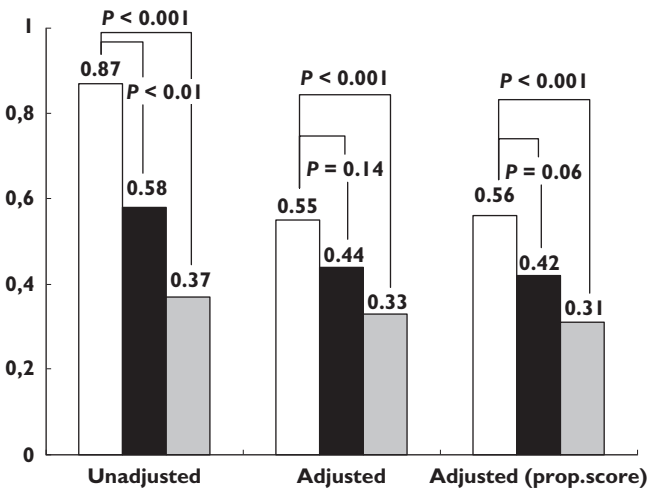

Figure 3

Hazard rates for the composite end-point of cardiovascular morbidity and cardiovascular mortality for subjects who started use of blood pressure-lowering drugs *vs.* subjects who did not start use of such agents. UAE, Urinary albumin excretion. On the left unadjusted hazard rates. In the middle adjusted hazard rates with adjustment for age, sex, body mass index (BMI), smoking, mean arterial pressure (MAP), cholesterol, glucose, serum creatinine, estimated glomerular filtration rate (eGFR), UAE, start of lipid-lowering drugs and blood glucose-lowering drugs. On the right adjusted hazard rates with adjustment for all previously mentioned variables, including propensity scores. *P*-values calculated using a χ^2 test (UAE < 15 mg day, □; UAE ≥ 15 mg day, ■; UAE ≥ 30 mg day, ▩)

placebo resulted in more absolute and relative CV risk reduction compared with placebo in subjects with higher pretreatment albuminuria [22]. Subgroup analysis of the HOPE Study has provided similar results [33]. This study included subjects at high CV risk and randomized them to placebo or the ACEi ramipril. The RR reduction obtained with the ACEi was greater in subjects who were microalbuminuria positive compared with subjects who were microalbuminuria negative. However, both the PREVEND IT study and the HOPE trial involved post hoc analyses and their observations were not formally tested. This was why we performed the present analyses with a predefined question. Another study has since been published that relates to these findings. The PEACE trial found that the ACEi trandolapril did not improve survival in the overall study population of patients with stable coronary artery disease and preserved systolic function [34]. However, in the subgroup of patients with reduced renal function the use of trandolapril was associated with a significant reduction in total mortality, as well as in CV outcome. It thus appears that, besides higher albuminuria, another marker of chronic kidney damage, i.e. lower renal function, shows an interaction with the use of blood pressure-lowering agents on outcome.

All three above-mentioned controlled trials (PREVEND-IT, HOPE, PEACE) concerned studies that randomized patients to placebo or an ACEi. Thus, it cannot be ascertained whether the interaction between treatment effect and albuminuria is specific to ACEis, or is just the result of blood pressure lowering of these drugs *per se*. In this

Table 4

Exposure to blood pressure-lowering drugs (at least one prescription*)

	All subjects (n = 765)	UAE < 15 mg day^{-1} (n = 320)	UAE ≥ 15 mg day^{-1} (n = 445)
All BPLDs			
<0.75 DDDs day^{-1}	453 (59.2%)	230 (71.9%)	223 (50.1%)
≥0.75 DDDs day^{-1}	312 (40.8%)	90 (28.1%)	222 (49.9%)
Non-ACEi/ARB only			
<0.75 DDDs day^{-1}	174 (79.5%)	100 (87.0%)	74 (71.2%)
≥0.75 DDDs day^{-1}	45 (20.5%)	15 (13.0%)	30 (28.8%)
ACEi/ARB only			
<0.75 DDDs day^{-1}	119 (76.8%)	48 (92.3%)	71 (68.9%)
≥0.75 DDDs day^{-1}	36 (23.2%)	4 (7.7%)	32 (30.1%)

*Subjects included can have received different blood pressure-lowering drugs during follow-up. BPLD, Blood pressure-lowering drugs; DDDs day^{-1}, defined daily dose per day; ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; UAE, urinary albumin excretion.

respect, our findings are of interest, suggesting that indeed ACEi/ARBs are superior to non-ACEi/ARBs in improving CV outcome in subjects with higher levels of albuminuria. A similar suggestion has been made by Reddan *et al.*, who found in subjects with an acute coronary syndrome an interaction between the effect of ACEis and glomerular filtration rate on 90-day mortality rate [35]. The lower renal function, the more protective ACE inhibition. In their analysis such an interaction was not found for other blood pressure-lowering drugs.

What might be the mechanism of our findings? Albuminuria has been shown to be closely correlated with endothelial damage due to atherosclerosis [36, 37]. In subjects with higher levels of albuminuria it is to be expected that a medical intervention that inhibits the progressive process of atherosclerosis, such as blood pressure lowering, will effectively prevent CV events. In contrast, subjects with low levels of albuminuria supposedly have little atherosclerosis. It might well be that in these latter subjects CV events are predominantly atherothrombosis related. It is less expected that the incidence of such events can be ameliorated by blood pressure lowering. Unfortunately, our dataset does not allow an in-depth analysis of this hypothesis, since it does not contain information on the pathophysiological origin of the CV events registered during follow-up.

Our present study, together with the supporting data from literature, may have important consequences. They suggest that in a subject without elevated levels of albuminuria on average the absolute risk for a CV event is relatively low, and that prescription of blood pressure-lowering drugs will hardly affect this absolute risk. In contrast, in hypertensive subjects with elevated levels of albuminuria the absolute risk for a CV event is high. Furthermore, it could be expected that in such patients the prescription of blood pressure-lowering agents, and especially ACEi/ARB, will result in significant relative, as well as absolute risk reduction.

A limitation of this study is its design. In contrast to randomized clinical trials (RCTs), observational studies are not the standard method to assess efficacy of medical intervention. Bias by indication and residual (unknown) confounding may play a role in observational studies. However, at the moment there are no RCTs designed to investigate prospectively the interaction between albuminuria levels and efficacy of blood pressure-lowering drugs. Furthermore, most RCTs have rigid inclusion and exclusion criteria that result in patient populations that are sometimes difficult to compare with broader groups of patients in real life. Therefore, results from clinical trial settings and a 'real-world' observational setting as in this study are of clinical relevance and should be regarded as additive to obtain a full picture of the effectiveness of blood pressure-lowering drugs [38]. To minimize the potential role of bias by indication a score was calculated for the propensity to be prescribed blood pressure-lowering medication. Our models were adjusted for this propensity score, as recommended for observational studies investigating the efficacy of medical intervention [29, 30]. Nevertheless, given its observational design, this study should be regarded as hypothesis generating rather than as hypothesis testing. Prospective RCTs, with *a priori* defined subgroup analyses according to UAE level and with tailored sample size, are needed to verify our findings.

The level of exposure to blood pressure-lowering drugs is another theoretical limitation. We noticed that the higher the level of albuminuria, the greater the level of exposure to blood pressure-lowering drugs. Theoretically, this could explain the higher efficacy of such drugs in preventing CV events in subjects with elevated albuminuria. However, in case our analyses were limited to only subjects with high exposure, it was again shown that efficacy of blood pressure was dependent on albuminuria before start of treatment with adjusted HRs of 0.46 and 0.27 (both $P < 0.01$) for UAE ≥ 15 mg day^{-1} and UAE ≥ 30 mg day^{-1}, respectively. Furthermore, in subgroup analyses adjust-

ment was made not only for baseline characteristics and propensity score, but also for level of exposure. We therefore think that our findings are robust.

In conclusion, our study has indicated that the efficacy of blood pressure-lowering agents to prevent CV events is dependent of the level of albuminuria before start of such treatment. The higher baseline albuminuria, the better the relative and absolute risk reduction for CV events with these drugs. These data suggest also that the CV protective effect of ACEi/ARBs in subjects with higher albuminuria may be better than that of other blood pressure-lowering agents. We caution that this was an observational study, and that these conclusions should therefore be regarded as hypothesis generating, rather than hypothesis testing.

The PREVEND Study has been made possible by grants of the Dutch Kidney Foundation. We thank Dade Behring (Marburg, Germany) for supplying equipment (Behring Nephelometer II) and reagents for nephelometric measurement of urinary albumin concentration.

REFERENCES

1 Guidelines Committee. 2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003; 21: 1011–53.

2 Withworth JA; World Health Organization International Society of Hypertension Writing Group. 2003 World Health Organization (WHO) /International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003; 21: 1983–92.

3 Cifkova R, Erdine S, Fagard R, Farsang C, Heagerty AM, Kiowski W, Kjeldsen S, Lüscher T, Mallion JM, Mancia G, Poulter N, Rahn KH, Rodicio JL, Ruilope LM, van Zwieten P, Waeber B, Williams B, Zanchetti A;ESH/ESC Hypertension Guidelines Committee. Practice guidelines for primary care physicians: ESH/ESC hypertension guidelines. J Hypertens 2003; 22: 1779–86.

4 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Roccella EJ;National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560–72.

5 Bakris G. Inclusion of albuminuria in hypertension and heart guidelines. Kidney Int Suppl 2004; 92: S124–5.

6 Pedrinelli R, Dell'Omo G, Di Bello V, Pontremoli R, Mariani M. Microalbuminuria, an integrated marker of cardiovascular risk in essential hypertension. J Hum Hypertens 2002; 16: 79–89.

7 Terpstra WF, May JF, Smit AJ, de Graeff PA, Crijns HJ. Microalbuminuria is related to marked end-organ damage in previously untreated, elderly, hypertensive patients. Blood Press 2002; 11: 84–90.

8 Verhave JC, Hillege HL, Burgerhof JGM, Navis G, de Zeeuw D, de Jong PE; Prevend Study Group. Cardiovascular risk factors are differently associated with urinary albumin excretion in men and women. J Am Soc Nephrol 2003; 14: 1330–5.

9 Tsioufis C, Dimitriades K, Antoniades D, Stefanadis C, Kallikazaros I. Inter-relationship of micro-albuminuria with the other surrogates of atherosclerotic cardiovascular disease in hypertensive subjects. Am J Hypertens 2004; 17: 470–6.

10 Palatini P. Microalbuminuria in hypertension. Curr Hypertens Rep 2003; 5: 208–14.

11 Campese VM, Bianchi S, Bigazzi R. Association between hyperlipidemia and microalbuminuria in essential hypertension. Kidney Int Suppl 1999; 56: S10–3.

12 Pontremoli R, Sofia A, Ravera M, Nicolella C, Viazzi F, Tirotta A, Ruello N, Tomolillo C, Castello C, Grillo G, Sacchi G, Deferrari G. Prevalence and clinical correlates of microalbuminuria in essential hypertension. The MAGIC Study. Hypertension 1997; 30: 1135–43.

13 Hillege HL, Janssen WMT, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, van Gilst WH, de Zeeuw D, de Jong PE; 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: 519–26.

14 Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. BMJ 1996; 313: 779–84.

15 Anavekar NS, Gans DJ, Berl T, Rohde RD, Cooper W, Bhaumik A, Hunsicker LG, Rouleau JL, Lewis JB, Rosendorff C, Porush JG, Drury PL, Esmatjes E, Raz I, Vanhille P, Locatelli F, Goldhaber S, Lewis EJ, Pfeffer MA. Predictors of cardiovascular events in patients with type 2 diabetic nephropathy and hypertension: a case for albuminuria. Kidney Int 2004; 66 (Suppl. 92): S50–5.

16 Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE, Prevention of Renal and Vascular Endstage Disease (Prevend) Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in the general population. Circulation 2002; 106: 1777–82.

17 Jager A, Kostens PJ, Ruhé HG, Heine RJ, Nijpels G, Dekker JM, Bouter JM, Stehouwer CD. Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: five year follow-up of the Hoorn Study. Arterioscl Thromb Vasc Biol 1999; 19: 617–24.

18 Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S, Hope Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001; 286: 421–6.

19 Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, Wareham NJ. A prospective study of microalbuminuria and incident coronary heart disease and its prognostic significance in a British population: the EPIC-Norfolk study. Am J Epidemiol 2004; 159: 284–93.

20 de Jong PE, Curhan GC. Screening, monitoring, and treatment of albuminuria: public health perspectives. J Am Soc Nephrol 2006; 17: 2120–6.

21 Basi S, Lewis JB. Microalbuminuria as a target to improve cardiovascular and renal outcomes. Am J Kidney Dis 2006; 47: 927–46.

22 Asselbergs FW, Diercks GFH, Hillege HL, van Boven AJ, Janssen WM, Voors AA, de Zeeuw D, de Jong PE, van Veldhuisen DJ, van Gilst WH, 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: 2809–16.

23 Pinto-Sietsma SJ, Janssen WM, Hillege HL, Navis G, de Zeeuw D, de Jong PE. Urinary albumin excretion is associated with renal function abnormalities in a nondiabetic population. J Am Soc Nephrol 2000; 11: 1882–8.

24 Pharmacy-dispensing database of IADB.nl. Available at http://www.iadb.nl (last accessed 20 July 2007)

25 Monster TB, Janssen WM, de Jong PE, de Jong-van den Berg LT, Prevend Study Group. Pharmacy data in epidemiological studies: an easy to obtain reliable tool. Pharmcoepidemiol Drug Saf 2002; 11: 379–84.

26 WHO Collaborating Centre for Drugs Statistics Methodology. ATC/DDD Index 2005. Available at http://www.whocc.no/atcddd (last accessed: 8 August 2007)

27 Prismant. National LHR information [in Dutch]. Available at http://www.prismant.nl [data specifically requested] (Last accessed: 8 June 2007)

28 http://www.cbs.nl/nl-NL/default.htm

29 Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on propensity score. J Am Stat Assoc 1984; 79: 516–24.

30 Cook EF, Goldman L. Asymmetric stratification. An outline for an efficient method for controlling confounding in cohort studies. Am J Epidemiol 1988; 127: 626–39.

31 Collins R, Peto R, Macmahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990; 335: 827–38.

32 Neal B, Macmahon S, Chapman N;Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Lancet 2000; 356: 1955–64.

33 Yusuf S, Sleight G, Pogue J, Bosch J, Davies R, Dagenais G; the Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342: 145–53.

34 Solomon SD, Rice MM, Jablonski KA, Jose P, Domanski M, Sabatine M, Gersh BJ, Rouleau J, Pfeffer MA, Braunwald E;Prevention of Events with ACE inhibition (PEACE) Investigators. Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the prevention of events with ACE inhibition (PEACE) trial. Circulation 2006; 114: 26–31.

35 Reddan DN, Szczech L, Bhapkar MV, Moliterno DJ, Califf RM, Ohman EM, Berger PB, Hochman JS, van der Werf F, Harrington RA, Newby LK. Renal function, concomitant medication use and outcomes following acute coronary syndromes. Nephrol Dial Transplant 2005; 20: 2105–12.

36 Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia 1989; 32: 219–26.

37 Verhave JC, Hillege HL, Burgerhof JG, Gansevoort RT, de Zeeuw D, de Jong PE; Prevend Study Group. The association between atherosclerotic risk factors and renal function in the general population. Kidney Int 2005; 67: 1967–73.

38 Vandenbroucke JP. Benefits and harms of drug treatments. Observational studies and randomised trials should learn from each other. BMJ 2004; 329: 2–3.