It’s all in a cup of “tea”

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by

Rudolph Schutte

Hypertension in Africa Research Team (HART)
Professor of Physiology
North-West University (Potchefstroom Campus)
South Africa
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Abstract

Background—Albuminuria as determined from easily collected spot urine or 24-hour urine samples reflects general vascular damage, associates with left ventricular hypertrophy, and predicts adverse cardiovascular and renal outcomes. However, this easily measurable and low cost marker of cardiovascular risk is not yet included in the European, American and South African hypertension guidelines and evidence in Africans is limited. Methods—We provide evidence of the usability of this marker in four papers from three different studies, i.e., the Sympathetic and Ambulatory and Ambulatory Blood Pressure in Africans (SABPA), the Prospective Urban Rural Epidemiological (PURE) study and the combination of the prospective ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and The Telmisartan Randomised AssessmeNt Study in ACE iNtoleranT subjects with cardiovascular Disease (TRANSCEND) trials. Results—In the SABPA study, urinary albumin excretion was higher in the Africans compared to the Caucasians, independent of blood pressure (P<0.01). In Africans, after adjustment for covariates, nighttime systolic blood pressure (β=0.347; P=0.003), diastolic blood pressure (β=0.298; P=0.010) and mean arterial pressure (β=0.331; P=0.004) correlated positively with albumin excretion. In addition, daytime (β=0.265; P=0.032) and nighttime (β=0.258; P=0.038) pulse pressure as well as pulse wave velocity (β=0.271; P=0.032) correlated positively with urinary albumin excretion. In hypertensives, the Cornell product (P=0.002), urinary albumin excretion (P=0.042), 24h systolic pressure (P<0.0001) and 24 pulse pressure (P<0.0001) was higher compared to normotensives. The Cornell product was associated with albumin excretion in single (r=0.25, P=0.012), partial (P trend=0.002) and multiple regression (β=0.301, P=0.002) analyses. In the PURE study, over a median follow-up of 4.52 years, 132 deaths occurred of which 47 were cardiovascular-related. In multivariable-adjusted analyses, urinary albumin excretion predicted all-cause mortality (hazard ratio, 1.26; 95% confidence interval, 1.07, 1.48; P=0.006), and a tendency existed for cardiovascular mortality (1.26; 0.97, 1.63; P=0.087), which seemed driven by fatal stroke (1.72; 1.17, 2.54; P=0.006) and not cardiac mortality (0.67; 0.41, 1.07; P=0.094). In the ONTARGET/TRANSCEND studies, patients with persistent normoalbuminuria (77.8%) had lower glucose values and systolic blood pressure when compared to patients with microalbuminuria at baseline or after 24 months. There was a strong association between albuminuria status and all-cause mortality, cardiovascular mortality and combined cardiovascular- and renal endpoints (all p<0.0001). Systolic blood pressure control and glucose status were less prominent risk predictors and even absent for all-cause (p≥0.23) and
cardiovascular mortality (p≥0.20). Irrespective of blood pressure control or glucose status, patients with improvement from microalbuminuria to normoalbuminuria after 2 years were at lower risk for all outcome measures than patients showing deterioration from normoalbuminuria to microalbuminuria. Those with diabetes, uncontrolled blood pressure and persistent microalbuminuria were at highest risk. **Conclusions**—In Africans, urinary albumin excretion associates with blood pressure, measures of arterial stiffness, left ventricular hypertrophy and predicts all-cause and cardiovascular mortality, especially stroke mortality. Improvement or lowering of urinary albumin excretion translates into decreased cardiovascular risk.
Introduction

The average life expectancy for people living in sub-Saharan Africa is 46 years compared to that of 78 years for the United States and 80 years for the United Kingdom. The current prominence of HIV infection and other infectious diseases such as tuberculosis and malaria in Africans contribute most significantly to this disturbing statistic. However, predictions are made that cardiovascular disease will soon eclipse infectious diseases as the leading cause of death and disability in sub-Saharan Africa. Indeed, high rates of hypertension and peripheral arterial disease observed in Africans behave in an explosive and debilitating manner with death occurring frequently from stroke, renal failure or congestive heart failure. In order to combat this trend, the early identification of high-risk subjects with subtle abnormalities in the cardiovascular system is important to curb the progression to cardiovascular disease through preventative treatment strategies.

Microalbuminuria is an established risk factor for cardiovascular morbidity and mortality and for end-stage renal disease, especially in individuals with hypertension and diabetes mellitus. It is regarded not only as a marker of glomerular endothelial damage, but also reflects general endothelial damage and relates to arterial stiffness and left ventricular hypertrophy. It therefore has prognostic significance and associates with increased cardiovascular risk in patients with diabetes, renal disease, hypertension and vascular disease, but also in normotensive non-diabetic individuals and in the general population. Even low-grade albuminuria has prognostic value and a reduction during treatment translates into reduction in cardiovascular events independent of in-treatment blood pressure level and therefore represents early progression of cardiovascular disease.

In light of the available evidence in Caucasian groups, urinary albumin excretion in Africans seems a prime candidate to be used by clinicians as a means to identify patients with early cardiovascular deterioration and at increased cardiovascular risk and subsequent initiation of appropriate intervention strategies. To our knowledge, associations between urinary albumin excretion and arterial stiffness, left ventricular hypertrophy and its predictive value for mortality is unknown in Africans.
Methods

Study Population

The detailed methods of the SABPA,\textsuperscript{27} PURE\textsuperscript{28} and ONTARGET/TRANSCEND studies\textsuperscript{29} are published elsewhere. In brief, the SABPA study was conducted between 2008 and 2009 and recruited 409 urbanised black and white educators working in the Dr Kenneth Kaunda district in the North West Province, South Africa. We invited all eligible participants between the ages of 25 and 65 years to participate. Exclusion criteria were an elevated ear temperature, psychotrophic substance dependence or abuse, regular blood donors and individuals vaccinated in the past three months. Cardiovascular measurements included 24-hour ambulatory blood pressure and electrocardiogram, pulse wave velocity and electrocardiographic left ventricular hypertrophy. Standard anthropometric measurements and physical activity was measured and basic biochemical measurements were performed including serum creatinine and urinary albumin from which the albumin-to-creatinine ratio was calculated to compensate for concentration differences of urine samples.

The PURE study tracks changes in lifestyle, cardiovascular disease risk factors, and chronic diseases in people from urban and rural areas of developing countries in transition. At baseline (2005), the South African leg included 2,010 randomly selected black South Africans, or hereafter referred to as Africans (1,004 urban and 1,006 rural) from the North-West Province. Participants invited were older than 35 years and reported the absence of any known diseases. Baseline measurements included sitting blood pressure, anthropometry and blood sampling. Over the five-year follow-up period we ascertained the vital status of participants. The cause of death was obtained from the family’s death certificate and verbal autopsy and coded by a physician according to the International Classification of Disease codes for the immediate and underlying causes. All people involved in these assessments were unaware of the participants’ albuminuria status. Cardiovascular mortality included all fatal cardiac and stroke events and death noted as “due to hypertension”. Death due to cardiac reasons included heart failure, myocardial infarction, congestive heart failure, or any other cardiac-related reason. Death due to stroke included any stroke or cerebral vascular incident.

The ONTARGET and TRANSCEND studies included 22,984 patients 55 years and older enrolled from 2001-2003. Patients had established atherosclerotic vascular disease, i.e. coronary, cerebrovascular or peripheral artery disease, or type 1 or type 2 diabetes with end-organ damage (retinopathy, left ventricular hypertrophy, micro- or macroalbuminuria), or any evidence of previous cardiac or vascular disease. Diabetes was defined as a fasting glucose > 125 mg/dl, or 2 hour oral glucose tolerance test >199 mg/dl or new diabetes reported by the
physician. Physician report of new onset of diabetes was based on the above-mentioned, as well as an HbA1c 1.1 times the upper limit of normal, or use of antihyperglycemic agents. The physician reports were not centrally adjudicated. Visits to the physician were every 6 months. Patients with new-onset diabetes during the first two years of the study were included. Patients with serum creatinine above 3.0 mg/dl, any known renal disease, renal artery stenosis, or, with uncontrolled hypertension (>160 mmHg systolic or > 100 mmHg diastolic) or with macroalbuminuria (> 300 mg/g creatinine) in TRANSCEND were excluded. Prior to inclusion in ONTARGET, two thirds of the study participants had received an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Patients intolerant to angiotensin converting enzyme inhibitors were included in the TRANSCEND study. The present study population included all patients with complete albuminuria data and glucose status over 2 years as well as available blood pressure measurements. The follow-up period for this analysis started at the second measurement of albuminuria at 24 months, and covered on average 32 months for the collection of outcomes. A central committee utilising standard definitions and blinded to treatment and albuminuria status adjudicated all main study outcomes (death, cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure). The primary composite cardiovascular outcome was death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. The composite renal outcome was defined as any dialysis or doubling of baseline serum creatinine.

All studies complied with all applicable requirements of international regulations, in particular the Helsinki declaration of 1975 (as revised in 2013) for investigation of human participants. The Ethics Review Board of the North-West University (Potchefstroom Campus) approved the study. Both the ONTARGET and TRANSCEND trials are registered at ClinicalTrials.gov number NCT00153101.

Results

Characteristics of Participants
In the SABPA study, urinary albumin excretion ($P<0.001$), daytime systolic ($P=0.002$), diastolic ($P<0.001$) and mean arterial pressure ($P<0.001$) as well as the nighttime systolic ($P<0.001$), diastolic ($P<0.001$) and mean arterial pressure ($P<0.001$) were higher in Africans compared to Caucasians (Figure 1). Seventy percent of the Africans and 52% of the Caucasians were hypertensive ($P=0.027$). Due to the higher blood pressure and hypertension prevalence in the Africans, we adjusted for 24h systolic and diastolic blood pressure and hypertension prevalence to see if urinary albumin excretion would still be higher in the African group. By doing so,
albumin excretion did indeed remain higher in the Africans (0.77 vs. 0.23 mg/mmol, \(P<0.001\)). In addition, we stratified the groups by 24h mean arterial pressure and adjusted for age and body mass index to compare albumin excretion between the ethnic groups at similar blood pressures (Figure 2). Again, urinary albumin excretion was higher \((P<0.01)\) in Africans at each category of 24h mean arterial pressure, confirming that this ethnic difference is independent of blood pressure. Lastly, kidney function was well within normal limits in the Africans.

**Figure 1** 24h systolic and diastolic blood pressure (95% confidence limits) of African and Caucasian men.

**Figure 2** Albumin-to-creatinine ratio and 24h mean arterial pressure by ethnicity and category of 24h mean arterial pressure adjusted for age and body mass index. Asterisk (*) denotes \(P\)-value less than 0.01 and ns, non-significant for differences between African and Caucasian men.
Unadjusted and Adjusted Analyses

In African men only (Table 1), we noticed significant positive associations of nighttime systolic blood pressure and mean arterial pressure with urinary albumin excretion while nighttime diastolic blood pressure and pulse pressure as well as pulse wave velocity tended to increase with increasing albumin excretion. These associations were confirmed in multiple regression analysis.

Table 1 Associations between ambulatory blood pressure, left ventricular hypertrophy and urinary albumin excretion in single regression analyses

<table>
<thead>
<tr>
<th>Albumin-to-creatinine ratio</th>
<th>African men</th>
<th>Caucasian men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daytime</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>$r=0.06; \ P=0.59$</td>
<td>$r=0.10; \ P=0.36$</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>$r=-0.05; \ P=0.71$</td>
<td>$r=0.16; \ P=0.12$</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>$r=0.001; \ P&gt;0.99$</td>
<td>$r=0.15; \ P=0.16$</td>
</tr>
<tr>
<td><strong>Nighttime</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>$r=0.26; \ P=0.032$</td>
<td>$r=0.02; \ P=0.83$</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>$r=0.21; \ P=0.081$</td>
<td>$r=0.03; \ P=0.79$</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>$r=0.24; \ P=0.047$</td>
<td>$r=0.027; \ P=0.80$</td>
</tr>
<tr>
<td><strong>Arterial stiffness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>$r=0.23; \ P=0.062$</td>
<td>$r=-0.09; \ P=0.38$</td>
</tr>
<tr>
<td>Daytime pulse pressure</td>
<td>$r=0.18; \ P=0.14$</td>
<td>$r=-0.05; \ P=0.67$</td>
</tr>
<tr>
<td>Nighttime pulse pressure</td>
<td>$r=0.20; \ P=0.094$</td>
<td>$r=0.003; \ P=0.98$</td>
</tr>
<tr>
<td>Cornell Product</td>
<td>$r=0.25; \ P=0.012$</td>
<td>$r=0.040; \ P=0.68$</td>
</tr>
</tbody>
</table>

The Cornell product correlated positively with urinary albumin excretion ($r=0.25, \ P=0.012$, Table 1, Figure 3), 24h systolic pressure ($r=0.22, \ P=0.030$) and 24h pulse pressure ($r=0.25, \ P=0.013$), but not with 24h diastolic pressure ($r=0.09, \ P=0.36$) in the hypertensives. None of these associations was present in the normotensive group ($r\leq0.20, \ P\geq0.16$) and excluded from further analyses.
In exploratory analyses, we plotted the Cornell product by quartiles of urinary albumin excretion while adjusting for age, gender and 24h systolic pressure (Figure 3). In doing so, the Cornell product increased with increasing albuminuria ($P_{\text{trend}}=0.002$). This association was also confirmed in multiple regression analysis with a 1-standard deviation increase in urinary albumin excretion associating with an 11.6 mV.ms increase in the Cornell product ($P=0.002$).

In the PURE study, the sex-, and age-standardised rates for all-cause ($P<0.0001$) and cardiovascular ($P=0.013$) mortality increased across tertiles of urinary albumin excretion. In analyses of Kaplan-Meier estimates, the log-rank test was significant for all-cause mortality (Figure 4A; $P=0.020$) and borderline significant for cardiovascular mortality (Figure 4B; $P=0.075$) across tertiles of urinary albumin excretion. The multivariable-adjusted standardized hazard ratios for mortality in relation to urinary albumin excretion are presented in Figure 5. Urinary albumin excretion predicted all-cause mortality (hazard ratios, 1.26; [95% confidence interval], 1.07 to 1.48; $P=0.006$), but a borderline significant association existed with cardiovascular mortality (1.26; 0.97–1.63; $P=0.087$). This relationship seemed driven by stroke mortality (1.72; 1.17–2.54; $P=0.006$), and not cardiac mortality (0.67; 0.41–1.07; $P=0.094$). We obtained similar results when excluding 10 participants with macroalbuminuria, but no relationship existed with the exclusion of microalbuminuric participants.

Figure 3 Associations between Cornell product and albumin-to-creatinine ratio in univariate and partial regression analyses, adjusted for age, gender and 24h systolic pressure. UACR, urinary albumin-to-creatinine ratio.
Figure 4 Kaplan-Meier survival function estimates for all-cause (A) and cardiovascular mortality (B) by tertiles of urinary albumin-to-creatinine ratio, PURE Study, South Africa, 2005-2010. P values refer to the significance of the log-rank test across 3 tertiles.

Figure 5 Adjusted standardized hazard ratios for endpoints in relation to the urinary albumin-to-creatinine ratio. The Cox models included age, body mass index, total cholesterol, gamma-glutamyltransferase, and physical activity as covariables. Hazard ratios are given with 95% confidence intervals.
In the ONTARGET/TRANSCEND studies a strong association existed between albuminuria status and mortality (all-cause and cardiovascular, p<.0001 for both outcomes). Compared to the group with persistent normoalbuminuria, all other groups had a significantly increased risk of death, with a more than 3-fold risk in patients with persistent microalbuminuria. When adjusted for confounders (Figure 6), the significant relationship was maintained, however, the risk increase in patients with microalbuminuria was a bit less pronounced. A weak relationship between glucose status and mortality that was seen in the unadjusted analysis (p=0.092 for all-cause, p=0.039 for CV mortality) disappeared when adjustment was made for the other confounders. Systolic blood pressure control consistently had no significant impact on mortality in unadjusted and unadjusted analysis.

Figure 6 Adjusted hazard ratios according to albuminuria-, glycaemia and blood pressure status. Albuminuria status is reflected by persistent normoalbuminuria (●); improvement from micro- to normoalbuminuria (●); deterioration from normo- to microalbuminuria (●); persistent microalbuminuria (●). Open symbols represent mean systolic blood pressure of <140 mmHg over 2 years and full symbols mean systolic blood pressure of ≥140 mmHg over 2 years. Reference group is persistent normoalbuminuria, fasting plasma glucose (FPG) persistently <100 mg/dl and a mean systolic blood pressure of <140 mmHg over 2 years. (For details see methods). The main effect COX regression model (with interaction between changes in albuminuria and baseline albuminuria included when significant) was used. *Hazard ratios were adjusted for age, gender, BMI, ethnicity, smoking, alcohol consumption, eGFR at baseline and eGFR change, mean diastolic BP and HR, study (ONTARGET, TRANSCEND), treatment, and diagnosis for study entry such as coronary artery disease, peripheral artery disease, previous stroke, transient ischemic attack or high-risk diabetes.
Consistently in unadjusted and adjusted analysis (Figure 6), albuminuria and glucose status had a strong impact on the combined cardiovascular outcome \((p<0.0001)\). There was also a significant association to systolic blood pressure control \((p=0.0038 \text{ (unadjusted), } p=0.0044 \text{ (adjusted)})\). All three effects act additively resulting in a hazard ratio of around 3 for the worst combination of persistent albuminuria, diabetes and insufficient systolic blood pressure control.

The results for the composite renal outcome are similar, with even higher risk increases in patients with persistent microalbuminuria. However, there is no significant effect of the glucose status when adjustment is made for other confounders.

**Discussion**

We investigated the relationships between measures of arterial stiffness, left ventricular hypertrophy and urinary albumin excretion in Africans and its possible role as marker of general vascular dysfunction. In addition, we investigated whether urinary albumin excretion predicts cardiovascular risk and whether a decrease in urinary albumin excretion over time translates into decreased cardiovascular risk. Although blood pressure was higher in Africans, albumin excretion was higher, independent of blood pressure. Measures of arterial stiffness, left ventricular hypertrophy and nighttime blood pressure were independently associated with urinary albumin excretion in Africans. Urinary albumin excretion also predicted all-cause and cardiovascular mortality and an improvement in albumin excretion after blockade of the renin angiotensin system translated into a decreased risk of having a cardiovascular event. The additive effects of a worsening of glucose status and being hypertensive were less pronounced than the albuminuria status over 2 years.

Our findings support previous prospective studies that included only Caucasian population groups. These studies showed that microalbuminuria \((>3.5 \text{ mg/mmol})\) and macroalbuminuria \((>30 \text{ mg/mmol})\) were associated with a higher risk of cardiovascular disease incidence and mortality in patients with hypertension\(^{30}\) or diabetes.\(^{31}\) Recently, Ärnlöv et al.\(^{22}\) reported that even low-grade urinary albumin excretion (mean urinary albumin excretion 1.21 mg/mmol) is associated with increased risk of cardiovascular disease and mortality in non-hypertensive, non-diabetic individuals and individuals with a low to intermediate pre-test probability of vascular events. They therefore supported the hypothesis that low-grade albuminuria in apparently healthy individuals may also be a marker of extra-renal subclinical vascular damage or dysfunction that predisposes to left ventricular hypertrophy, future cardiovascular disease and death.\(^{22}\) This is also supported by our associations obtained in Africans with a mean urinary albumin excretion of 0.79 mg/mmol, well below the diagnostic threshold for microalbuminuria.\(^{32}\)
Available evidence regarding the relationship between left ventricular hypertrophy and urinary albumin excretion is inconsistent and from selective groups. Palatini et al.\textsuperscript{33} could not obtain this association in relatively young stage I hypertensives with a mean age $\approx$31 years. However, other groups were successful, but mostly in patients with microalbuminuria or diagnosed left ventricular hypertrophy or both. Leoncini et al.\textsuperscript{34} reported a univariate correlation in 346 never-treated non-diabetic hypertensive patients. Also in never-treated non-diabetic hypertensive men, Del'Omo et al.\textsuperscript{35} reported an adjusted increase in relative risk for developing microalbuminuria with increasing left ventricular hypertrophy. Wachtell et al.\textsuperscript{36} found a link in 8029 patients including diabetics with stage II and III hypertension with diagnosed LVH of which 23% had microalbuminuria and 4% macroalbuminuria. Evidence in Africans however, is limited and contradictory. Busari et al.\textsuperscript{37} found left ventricular hypertrophy to be more common in 96 non-diabetic hypertensives with microalbuminuria compared to those without and reported a univariate correlation between left ventricular hypertrophy and albuminuria. Also in univariate analysis, Mbanya et al.\textsuperscript{38} reported this relationship in 40 normotensive type 2 diabetic patients. Post et al.\textsuperscript{39} provided adjusted evidence in 109 young (mean age 41 years) hypertensive black American men in multiple regression analysis in which blood pressure was included in the models. On the other hand, this relationship was absent in 1091 black South African patients recruited from 100 private practices in logistic regression analysis.\textsuperscript{40} Surprisingly, in the context of a clinical trial, Peterson et al.\textsuperscript{41} could also not obtain the left ventricular hypertrophy-albuminuria relationship in multiple regression analysis involving 599 aged non-diabetic hypertensive black Americans with renal disease.

We obtained a relationship with all-cause mortality and stroke, but not cardiac mortality. Stroke mortality seemed to drive the relationship between urinary albumin excretion and cardiovascular mortality. The relationship between cardiac mortality and urinary albumin excretion is complex. Some studies report that albuminuria predicts mortality in patients with heart failure and left ventricular hypertrophy,\textsuperscript{12,42,43} but predictive evidence also exists for heart failure in subjects initially free of heart failure.\textsuperscript{44} However, to date no sound mechanistic explanation exists for this relationship. The most generally excepted is that endothelial damage at the glomeruli resulting in albumin leakage also reflects systemic endothelial damage\textsuperscript{45} and therefore the initial stage of the atherosclerosis/arteriosclerosis process. As the relationship between albuminuria and arterial stiffness is known in Africans\textsuperscript{27} and other populations,\textsuperscript{46,47} the mechanism linking albuminuria to heart failure seems more indirect through the known arterial stiffness – cardiac afterload – left ventricular hypertrophy pathway.\textsuperscript{48} On the other hand, a more direct relationship exists between albuminuria and coronary artery disease, as endothelial
dysfunction can directly lead to a coronary event.\textsuperscript{49,50} Indeed, human studies demonstrated a relationship between microalbuminuria and the presence and severity of coronary artery disease\textsuperscript{51} and that even low levels of albuminuria predicts coronary events and death.\textsuperscript{52} However, coronary artery disease is less common in Africans. As part of the Heart of Soweto Study, Sliwa et al.\textsuperscript{10} determined in 1593 newly diagnosed patients with cardiovascular disease, that Africans were more likely to be diagnosed with heart failure than the rest of the cohort (odds ratio 1.46, 1.11–1.94), but less likely with coronary artery disease (odds ratio 0.10, 0.07–0.14). In the current study, type of cardiac death was not specified. One could speculate that the possible less direct association between albuminuria and heart failure, and the lower probability of coronary events in Africans, may explain the observed absence of an association between allbuminuria and cardiac mortality. The relationship with stroke on the other hand, as with coronary events, seems more direct. This is supported by the observed close relationships between microalbuminuria and cerebral small vessel disease as determined by neuroimaging\textsuperscript{15,53} and increased vascular risk as shown in stroke survivors.\textsuperscript{54}

There is accumulating evidence on the prognostic significance of change in albuminuria over time. Especially in diabetes, available evidence is limited and questionable.\textsuperscript{25,55-58} Spoelstra-de Man et al.\textsuperscript{55} found predictive value in an increase in urinary albumin excretion over 2 years for mortality mainly from coronary heart disease after 4 years of follow-up. However, this small study included 58 type 2 diabetic and microalbuminuric patients in which only 5 coronary and 7 all-cause fatalities occurred. Similarly, an increase of albuminuria over 1 year predicted mortality and cardiovascular disease in 161 type 1 and 266 type 2 diabetic patients with overt nephropathy (urinary albumin excretion $\geq$30 mg/24h).\textsuperscript{56} Amongst the first to report reduced risk in diabetes due to a decrease in urinary albumin excretion over time, comes from the Reduction in Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study. After 3.4 years follow-up, this study reported an 18% reduction in cardiovascular risk and a 27% reduction in heart failure risk for every 50% reduction in albuminuria after 6 months in 1513 type 2 diabetic patients with nephropathy randomized to losartan treatment.\textsuperscript{25} Of note, the study population had overt proteinuria and chronic renal failure, thus an advanced stage of diabetic disease. Recently, Estacio et al.\textsuperscript{58} compared the 10-year mortality rates of a decrease and increase of 2 logs in urinary albumin excretion after 1 year, and found lower mortality rates for a 2 log decrease (4.7% vs. 24.5%) in 393 type 2 diabetic patients in which 47 cardiovascular deaths occurred. Similar to our study, the authors\textsuperscript{58} included patients with normo-, micro-, and macroalbuminuria. Of the 22984 patients, our study included 8454 (36.8%) patients with diabetes and 8283 (36.0%) hypertensives and found that the additive
effects of diabetes and hypertension were less pronounced than albuminuria status and its change. Nevertheless, and in accordance with other studies, cardiovascular risk was the highest in patients with diabetes, combined with persistent microalbuminuria, and hypertension.

Our findings have important clinical implications. The rate of progression of urinary albumin excretion over time gives additional information of deterioration or improvement of vascular disease and therefore increased or decreased cardiovascular risk. The fact that the prognostic significance of urinary albumin excretion was independent of diastolic blood pressure, suggest that reduction in urinary albumin excretion over time may be a target for treatment in addition to blood pressure. Indeed, evidence of effective treatment strategies involving blocking of the renin-angiotensin system exists, where lowering of albuminuria is achieved independent of the blood pressure lowering effect of drugs. The European Society of Hypertension guidelines also recommend the testing for microalbuminuria in the management of hypertension and acknowledges that changes in albuminuria have "moderate" prognostic value. The implications of our findings are therefore that by evaluating the dynamics of albuminuria over time, especially in diabetic patients, can become an invaluable monitoring tool that will assist clinicians in following patients with diabetes on treatment and with increased cardiovascular risk.

In conclusion, urinary albumin excretion associated with increased blood pressure, arterial stiffness, and left ventricular hypertrophy. Urinary albumin excretion also predicts cardiovascular events, but more importantly that a reduction in albuminuria over time translates into a reduced likelihood of having a cardiovascular event. Urinary albumin excretion therefore seems to be an excellent marker for increased cardiovascular risk and should be monitored by clinicians to evaluate the effectiveness of intervention strategies.
References


16. Liu CS, Pi-Sunyer FX, Li CI et al. Albuminuria is strongly associated with arterial stiffness, especially in diabetic or hypertensive subjects--a population-based study (Taichung Community Health Study; TCHS). *Atherosclerosis* 2010; 211:315-21.


