Editorial Commentary

Urinary Albumin Excretion
Lowering the Threshold of Risk in Hypertension

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During the past few years, a subtle increase in urinary albumin excretion (UAE) not detectable by routine methods, microalbuminuria, has become a prognostic marker for cardiovascular and/or renal risk in diabetic and nondiabetic subjects. Consequently, microalbuminuria assessment is now recommended in a risk stratification strategy not only in diabetic subjects but also for hypertension management. Microalbuminuria is defined as UAE from 30 to 300 mg/24 hours or equivalent amounts using timed overnight or spot urine samples (Table). The definition comes from studies that have established its value as a marker of risk for nephropathy in diabetic subjects. When the potential prognostic value of microalbuminuria on cardiovascular disease was being assessed in diabetic and nondiabetic populations, the threshold value pointing to an increment of risk was largely below the UAE value of 30 mg/24 hours regardless of the population studied.\(^1\) Dammsgard\(^2\) in an elderly population demonstrated that subjects with timed overnight UAE >7.5 \(\mu g/min\) had a higher mortality rate than those with lower values. Borch-Johnsen\(^1\) found, in a population-based cohort of 2085 consecutive subjects, the relative risk of ischemic heart disease associated with an spot urine albumin/creatinine ratio of only >0.65 mg/mmol was 2.3 when adjusted for other risk factors. Likewise, Jager, in the Hoorn study,\(^4\) a population-based cohort aged 50 to 75 years followed-up prospectively for 5 years, albumin/creatinine ratio >2.0 mg/mmol in a spot urine was associated with a 4-fold increase in cardiovascular mortality and \(\approx 2\)-fold increase in all-cause mortality. Furthermore, in a cohort of postmenopausal women living in Utrecht,\(^5\) the cardiovascular age-adjusted mortality rate for hypertensive women who were in the highest quintile of UAE was 4.3-times greater than that observed in women without detectable UAE. The highest quintile corresponded to an albumin/creatinine ratio >2.41 mg/mmol. Finally, in the cohort of subjects included in the HOPE study,\(^6\) compared with the lowest quartile of albumin/creatinine ratio, the relative risk of the primary end point in the fourth quartile, defined as albumin/creatinine ratio >1.62 mg/mmol, was 1.97.

Klausen et al,\(^7\) in this issue, have delved deeply at this point, not only in looking for a threshold for risk but also in calculating risk along a wide range of UAE. They have observed that hypertensive subjects with a timed overnight UAE >5 \(\mu g/min\) have an increased risk for total mortality and coronary heart disease. The risk of coronary heart disease and mortality significantly increases 70% and 50%, respectively, when the UAE is between 5 and 10 \(\mu g/min\), and 100% for both when the UAE is >10 \(\mu g/min\). In their study, increments of risks are independent of the factors that are known to influence the presence of microalbuminuria: age, blood pressure levels, smoking, body mass index, diabetes, creatinine clearance, or total or high density lipoprotein cholesterol. Even though UAE was only measured once, it was performed in timed overnight samples, which are among the most reproducible.

Two recently published studies have also shed light on our knowledge of microalbuminuria in hypertension populations and how it can be managed.\(^8\) In one study by our group, subjects with an initial UAE level in the high-normal range, from 15 to 29 mg/24 hours, have an increased risk of progressing toward microalbuminuria. The development of microalbuminuria is linked to insufficient blood pressure control and to a progressive increment of glucose values. Thus, appropriate intervention may reduce the progressive increment of UAE. Ibsen et al\(^9\) in the LIFE study find that baseline and in-treatment levels of albuminuria are powerful predictors for subsequent cardiovascular morbidity and mortality. Reduction in albuminuria during treatment translates into a reduction in cardiovascular events. Although the units by which UAE have been expressed differ among the 3 studies, the 5 \(\mu g/min\) from Klausen is close to the 15 mg/24 hours from our study, in which there was an increased risk for UAE to increase over time, and to the 1 mg/mmol of creatinine in a morning urine spot, corresponding to the second strata of risk in the Ibsen study.

Until studies specifically designed to answer whether UAE may be used as an intermediate endpoint to monitor the success of a reduction in cardiovascular and renal risk are available such in diabetes,\(^10\) how can this new information influence daily clinical practice? The 3 studies pointed to monitoring of albuminuria as an integrated part of the management of hypertension.

In diabetic and nondiabetic subjects, the continuous relationship between UAE and cardiovascular risk raises the question of the value of UAE when there is a substantial increment of risk and, consequently, when intervention is justified. Furthermore, what should be the UAE goal during intervention? Defining the risk of microalbuminuria at an early stage, such as at the threshold established in the Klausen...
study, would be adequate for guiding therapies geared to preventing progression of UAE. If albuminuria is not decreased by a patient’s current antihypertensive and/or other treatment, further intervention directed toward blood pressure control and other modifiable risks should be considered.

Finally, Klausen et al propose in the title of their article “a new definition of microalbuminuria in hypertensive subjects.” The use of the term microalbuminuria as defined by different values according to the disease considered, eg, diabetes or hypertension, diseases that are closely linked to each other may be misleading. The use of UAE, avoiding categorization with a given threshold, should be encouraged.

The assessment of subtle increases in UAE is a powerful way to identify those at risk for multiple cardiovascular risk factor intervention. Changes in UAE seem to run in parallel to cardiovascular risk, and prompt intervention to avoid the progressive increment of UAE may result in better protection against hypertension-induced morbidity and mortality. Although some pieces of information remain to be found, UAE has come of age in the arena of hypertension.

### Current Criteria to Define Microalbuminuria According to the Urine Sample

<table>
<thead>
<tr>
<th>Units</th>
<th>Spot</th>
<th>Timed Overnight</th>
<th>24-Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/24 h</td>
<td>30–299</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/min</td>
<td>20–199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/mmol Cr</td>
<td>3–29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/mg Cr</td>
<td>30–299</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cr indicates creatinine.

### References
