Evaluation of Subclinical Organ Damage for Risk Assessment and Treatment in the Hypertensive Patient: Role of Microalbuminuria

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Microalbuminuria, i.e., abnormal urinary excretion of albumin, which is detectable by low cost and widely available tests, is a first-line tool for identifying hypertensive patients who are at higher cardiovascular (CV) risk. Numerous studies have provided evidence that microalbuminuria is a concomitant of cardiac and vascular damage as well as a strong, independent predictor of CV events. An important, emerging issue is that the risk for CV morbidity and mortality is linearly related to urinary albumin excretion and persists well below the currently used cutoff for defining microalbuminuria. Furthermore, late-breaking evidence suggests that a reduction of albuminuria under antihypertensive treatment is paralleled by changes in urinary albumin excretion and persists well below the currently used cutoff for defining microalbuminuria. Furthermore, an important, emerging issue is that the risk for CV morbidity and mortality is linearly related to urinary albumin excretion and persists well below the currently used cutoff for defining microalbuminuria. Microalbuminuria, whose prevalence ranges from 5 to 40%, is a first-line tool for identifying hypertensive patients who are at higher cardiovascular (CV) risk. Numerous studies have provided evidence that microalbuminuria is a concomitant of cardiac and vascular damage as well as a strong, independent predictor of CV events. An important, emerging issue is that the risk for CV morbidity and mortality is linearly related to urinary albumin excretion and persists well below the currently used cutoff for defining microalbuminuria. Microalbuminuria, whose prevalence ranges from 5 to 40%, is a first-line tool for identifying hypertensive patients who are at higher cardiovascular (CV) risk. Numerous studies have provided evidence that microalbuminuria is a concomitant of cardiac and vascular damage as well as a strong, independent predictor of CV events. An important, emerging issue is that the risk for CV morbidity and mortality is linearly related to urinary albumin excretion and persists well below the currently used cutoff for defining microalbuminuria.

Microalbuminuria as a Marker of CV Risk

Cardiovascular diseases are the leading cause of death in Western countries, accounting for more than one third of all deaths. This is due mainly to the steady increase in the prevalence of hypertension and diabetes, which affect 30 and 8% of the general population, respectively, and have now reached the proportion of a worldwide epidemic. Unfortunately, the prevalence rates of these abnormalities are expected to increase in the next 2 decades, resulting in a further rise in the number of deaths from cardiovascular (CV) complications (1,2). A similar scenario mandates the need for both better implementation of antihypertensive treatment and early identification of patients who are at increased CV risk.

The assessment of global risk profile, including the severity of hypertension and the presence of concomitant CV risk factors, represents a prerequisite for devising effective antihypertensive treatment (3). The National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study showed that reducing a given BP (by approximately 12 mmHg) over a 10-yr period is much more beneficial in patients with a worse global risk profile (4). Recently, international hypertension guidelines acknowledged the relevance of minor abnormalities in renal function for stratifying patients with arterial hypertension. The Seventh Report of the Joint National Committee, for example, considers the presence of microalbuminuria or a slight reduction in GFR (<60 ml/min) as major CV risk factors (5). European guidelines go even further and list a slight elevation in serum creatinine (>1.3 mg/dl in men and 1.2 mg/dl in women) and/or the presence of microalbuminuria among the signs of hypertensive organ damage (3). This brief review focuses on the role of microalbuminuria as an integrated marker of subclinical organ damage and its usefulness for global risk assessment and effective treatment.

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Microalbuminuria as a Marker of CV Risk

The occurrence of microalbuminuria in patients who do not have diabetes but have primary hypertension was first described by Parving et al. (6) in 1974. Although 24-h urine collection is still considered the reference method for measuring urinary albumin excretion, evaluating the albumin to creatinine ratio in a first morning urine sample is easier but no less accurate and has rapidly become the method of choice in clinical practice. Since 1974, several studies have shown that microalbuminuria, whose prevalence ranges from 5 to 40%, is a useful tool when evaluating CV risk in hypertensive patients. We and others have demonstrated that microalbuminuria is associated with extrarenal signs of hypertensive target organ damage, such as left ventricular hypertrophy and carotid atherosclerosis (7). Furthermore, a large body of data indicate that microalbuminuria is a strong, independent predictor of CV events both in patients with and in patients without diabetes.

An important, emerging issue is that the risk for CV morbidity and mortality is linearly related to urinary albumin excretion, without any recognizable threshold or plateau. In the LIFE study, for example, the rate of the primary composite end point increased linearly four- to five-fold in patients from the lowest to the highest deciles of the albumin to creatinine ratio (8). On the basis of these findings, it was suggested recently that the cutoff value for defining microalbuminuria in essential hypertension be lowered to improve diagnostic sensitivity (9).
Late-breaking evidence suggests that a reduction of albuminuria under antihypertensive treatment is paralleled by changes in CV risk. In the LIFE study, baseline and in-treatment values of albuminuria were classified into four increasing categories that were added as time-varying covariates in Cox regression models. Hazard ratios for in-treatment albuminuria also were calculated. Therefore, the risk for each albuminuria category changed over time and patients shifted among the different classes as their albumin to creatinine ratio levels changed during the study period. It is interesting that this analysis provided proof that when albuminuria decreased during treatment, the risk for the primary composite end point also was reduced, suggesting that changes in albuminuria translate to changes in risk (10). These results led the authors to suggest that reducing albuminuria might become a therapeutic goal in itself.

The finding that a reduction in albuminuria parallels an improvement in CV prognosis supports, at least in part, the concept that microalbuminuria may be a CV risk factor rather than simply a risk marker. It is noteworthy that the prognostic role of albuminuria seems to be even stronger than that of left ventricular mass, at least with regard to the occurrence of CV mortality. In fact, in the LIFE study, albuminuria and left ventricular mass proved to be independent of each other and additive in predicting CV outcomes (11). However, in Cox regression analysis, adjusting for traditional CV risk factors, albuminuria but not left ventricular hypertrophy predicted the composite end point.

**Usefulness of Microalbuminuria in Clinical Practice**

The likelihood of identifying cardiac and vascular subclinical abnormalities in clinical practice strongly depends on the diagnostic techniques that are used. We and others previously demonstrated that the percentage of patients who are allocated to high/very high risk classes increases progressively according to the number of diagnostic tests that are performed on each patient (12). Undoubtedly, the widespread use of sensitive diagnostic tests such as ultrasound scans of the cardiac and vascular structures in the search for left ventricular hypertrophy and carotid abnormalities is a good option. However, because of the high prevalence of hypertension, this approach may not always be implemented in clinical practice because of both logistic and financial reasons.

We provided evidence to support the routine search for microalbuminuria in hypertensive patients as a cost-effective approach to the stratification of global risk. First, by means of albuminuria and an artificial neural network, we demonstrated that hypertensive patients can be placed into different risk classes with a degree of accuracy that is almost superimposable to what can be obtained by assessing target organ damage by ultrasound scan but at a significantly lower cost (13). Second, by showing that different signs of target organ damage only partly cluster and that microalbuminuria is an integrated marker of target organ damage, we showed that the routine search for microalbuminuria might lead to optimization of the diagnostic workup (12). Because the relationship between albuminuria and left ventricular mass is linear over the entire range, adopting a lower cutoff value for albuminuria might further improve the cost-effectiveness of CV risk stratification. Such a hypothesis certainly is worth testing in the clinical setting.

**Conclusion**

The evaluation of urinary albumin excretion represents an important part of the management of hypertension, even in younger patients. Microalbuminuria should be assessed before treatment is started to optimize the diagnostic workup and during antihypertensive therapy to monitor the effectiveness of treatment even beyond BP control.

**References**

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