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Microalbuminuria and Cardiovascular Risk Assessment in Primary Hypertension: Should Threshold Levels Be Revised?

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Background: Urinary albumin excretion and left ventricular mass are related to each other and to the risk of cardiovascular events in patients with primary hypertension. We aimed to identify a lower threshold for albuminuria that might improve detection of patients with left ventricular hypertrophy (LVH) and cost-effectiveness in cardiovascular risk assessment.

Methods: Albuminuria and left ventricular mass index were assessed in 448 untreated, nondiabetic patients with primary hypertension. The impact that lower albuminuria cut-off levels might have on detecting LVH was evaluated with regard to test cost and sensitivity. This was done by a diagnostic algorithm consisting of albuminuria evaluation followed by echocardiography in the presence of normoalbuminuria.

Results: The area under the ROC curve of albuminuria in predicting LVH was 0.73. Using a lower albumin to creatinine ratio threshold than what is recommended by the guidelines (ie, 11.5 mg/g), the sensitivity and specificity of albuminuria in identifying patients with LVH was 39% and 92%, respectively, which translated to positive and negative predictive values of 76% and 69%, respectively. When considering only patients without electrocardiographically detected LVH, routine screening for albuminuria, followed by echocardiography in the presence of albuminuria $\leq$11.5 mg/g, allowed us to decrease the number of echocardiograms by 23%.

Conclusion: Adopting a lower threshold to define microalbuminuria could prove to be cost-effective for assessing cardiovascular risk in hypertensive patients. Am J Hypertens 2006;19:728–734 © 2006 American Journal of Hypertension, Ltd.

Key Words: Albuminuria, hypertrophy (heart), receiver operating characteristic curve, cost-effectiveness, risk factors, global assessment.

Accurate risk stratification plays a critical role in devising therapeutic strategies for patients with primary hypertension.[1,2] In particular, detecting left ventricular hypertrophy (LVH), a powerful, independent predictor of cardiovascular morbidity and mortality[3,4] has a major impact on the global burden of risk.[1] The likelihood of identifying LVH, however, very much depends on the diagnostic test that is used in clinical practice, with both the electrocardiogram and echocardiogram showing good specificity, but different degrees of sensitivity.[5] A more widespread use of the echocardiogram could lead to the identification of a greater number of patients with LVH.[6] However this is not always feasible from a logistic and financial point of view when we take into consideration the high prevalence of hypertension.[7]

Microalbuminuria is another widely available and cost-effective marker of cardiovascular risk.[7] Very recently it has been shown that the relationship between urinary albumin excretion and cardiovascular risk extends well below the threshold that is currently used to define microalbuminuria.[8,9] Furthermore urinary albumin excretion is linearly related to left ventricular mass,[8,10] and changes in albuminuria over time have

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been shown to parallel those in left ventricular mass in hypertensive patients.[11]

Thus it has been argued that adopting cut-off values lower than the ones recommended by the European Society of Hypertension Guidelines to identify microalbuminuria might be advisable so as to increase sensitivity in indentifying individuals at high risk.

In this study we evaluated the relationship between urinary albumin excretion and left ventricular mass index to identify a lower threshold of albuminuria that might improve the cost-effectiveness of cardiovascular risk assessment.

Methods

Study Population

Between January 2001 and January 2005, all untreated patients with primary hypertension attending the outpatient clinic at our institution were asked to participate in the present study, which was part of a larger trial (Microalbuminuria: A Genoa Investigation on Complications [MAGIC]) approved by the Ethical Committee of our Department. Details of the study have already been published.[12] Exclusion criteria included the presence of neoplastic, hepatic or renal disease, chronic heart failure (New York Heart Association class III and IV), positive history or clinical signs of ischemic heart disease, diabetes mellitus, severe obesity (defined as body weight >150% of ideal body weight), or disabling diseases such as dementia or inability to cooperate. Diagnosis of essential hypertension was made by the attending physician after complete medical history, physical examination, and routine biochemical analyses of blood and urine (including urine sediment evaluation) were obtained from each patient. Further investigation was carried out only when abnormalities were found in these analyses or when other symptoms or signs suggesting secondary hypertension were present. Hypertension was defined as an average blood pressure (BP) ≥140/90 mm Hg on at least two different occasions. None of the patients were taking medication at the time of the study. Altogether 534 untreated patients with primary hypertension were seen at our clinic within the period mentioned above, and among them 491 (92%) were eligible for the study on the basis of available clinical and laboratory data. Eighteen of these patients did not meet study criteria based on the results of additional tests prescribed for clinical reasons during their first visit to our clinic. Among the remaining 473 patients (all Europeans of white ethnicity), 25 were excluded because they declined (14 of 25) or because of inadequate quality of echocardiographic images (11 of 25); and 448 form the basis of the present report. Of the participating patients, 381 (85%) had never been treated for hypertension, whereas 67 (15%) had received antihypertensive treatment in the past, albeit intermittently and not during the 6 months before the study. After written informed consent had been obtained, all patients underwent the following procedures: office BP measurement, blood and urine sampling, standard 12-lead electrocardiography, echocardiography, and carotid ultrasonography. On the study day, after an overnight fast, height and weight were measured and venous blood was drawn for measurement of hematochemical parameters. Blood pressure was measured by a trained nurse using a mercury sphygmomanometer (cuff size 12.5 × 40 cm), with the patient in the sitting position after a 5-min rest. The systolic and diastolic BP were read to the nearest 2 mm Hg. Disappearance of Korotkoff sounds (phase V) was the criterion for diastolic BP. Three consecutive readings were performed and the average was recorded. Body mass index was calculated as weight (kg) / height^2 (m^2). Creatinine, blood urea nitrogen, electrolytes, uric acid, triglycerides, total and high-density lipoprotein (HDL) cholesterol, and other standard blood chemistry evaluations were performed on serum according to routine methods. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedwald formula.[13] Family history and lifestyle habits were assessed by means of a standard questionnaire. Creatinine clearance was estimated by the Cockcroft-Gault formula[14] and normalized for body surface area. Ideal body weight was used in the formula.

Electrocardiography

Standard electrocardiograms were evaluated to detect LVH, defined as the presence of at least one of two electrocardiographic criteria: the Sokolow–Lyon voltage[15] and the gender-specific Cornell voltage–duration product.[16]

Albuminuria

Albuminuria was evaluated in each patient by measuring the albumin-to-creatinine ratio. The mean of two nonconsecutive first-morning samples was recorded. Only samples from patients with negative urine cultures were collected. The albumin-to-creatinine ratio was calculated as urine albumin concentration (mg/L) / urine creatinine concentration (g/L).[12] Urine albumin concentration was measured using a commercially available radioimmunoassay kit (Pantec, Torino, Italy). Microalbuminuria was defined as an albumin to creatinine ratio ≥22 mg/g in men and ≥31 mg/g in women.

Echocardiography

All echocardiographic studies were performed using an Acuson Sequoia C-256 ultrasound machine (Acuson Corp., Mountain View, CA). The overall one-dimensional left ventricular measurements and the two-dimensional (apical four- and two-chamber) views were obtained according to the recommendations of the American Society of Echocardiography.[17] The left ventricular mass was derived using the formula described by Devereux et al.[17] The