Role of Microalbuminurin in the Assessment of Cardiovascular Risk in Essential Hypertension

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Accurate cardiovascular risk evaluation is a prerequisite for devising cost-effective therapeutic strategies in patients with essential hypertension. In fact, the knowledge of concomitant risk factors, diabetes, target organ damage, or associated clinical conditions may be useful when deciding both treatment and BP goals. Thorough evaluation of target organ damage is the key to sensitive assessment of global risk, but cost-effective allocation of economic resources should also be taken into consideration. Thanks to its low cost and widespread availability, the search for microalbuminuria is a first-line tool for identifying hypertensive patients who are at higher cardiovascular risk.

The prevalence of hypertension has increased over the past decade, reaching an alarming level of 25% among the general population in the United States and an even higher percentage in Europe (1). Despite overwhelming evidence that effective treatment of hypertension is associated with a significant reduction of cardiovascular events, the number of patients who are aware of their condition and who achieve adequate BP control remains unacceptably low (2). This issue has now become a major public health problem that needs to be faced with more aggressive treatment strategies to contain the incumbent epidemic of cardiovascular complications. The key issue when dealing with such a large number of patients is the ability to identify and target the subgroup at higher risk for future events.

Rationale for Global Risk Assessment in Essential Hypertension

Over the past several years the concept that global risk, rather than the severity of hypertension alone, should be taken into consideration when devising therapeutic strategies has become more and more accepted (3). The rationale for a similar approach is well demonstrated by an analysis of the data from the National Health and Nutrition Examination Survey study, which show a remarkable improvement in cost-effectiveness when treating patients with progressively worsening global risk profile at any given BP level (4). Accordingly, one would have to treat approximately 500 low-risk patients with borderline hypertension, lowering BP by approximately 12 mmHg over 10 yr, to prevent one cardiovascular event. While the number needed to treat becomes smaller in the subgroup of patients with more severe hypertension, it decreases even further in those with multiple risk factors and/or target organ damage. In fact, the relationship between cardiovascular mortality and BP reduction is strongly influenced by the global burden of risk in each patient. As a consequence, even reaching optimal BP levels may not convey adequate protection from the incidence of morbid events in patients who are at highest risk. Additional therapeutic measures aimed at optimizing glycometabolic control and lipid levels, along with antiplatelet treatment (if not contraindicated), are helpful and should be implemented. Such an integrated, multifactorial therapeutic approach proved to be very effective in the Steno II study, wherein hypertensive patients with type 2 diabetes and microalbuminuria were randomized to receive either standard care or more intensive, multifactorial treatment with antihypertensive drugs (preferably renin angiotensin system inhibitors), aspirin, and statins (5). Over an 8-yr follow-up, a significant improvement in outcome was evident both for macro- and microvascular complications in patients who underwent more aggressive treatment. Thus, global risk assessment seems to be of paramount importance for hypertensive patients. In fact, it may be useful both when deciding whether to start treatment and for setting appropriate goals.

Microalbuminuria as an Integrated Marker of Cardiovascular Risk

An association between microalbuminuria and several cardiovascular risk factors, such as BP load, dyslipidemia, endothelial dysfunction, insulin resistance, salt sensitivity, and increased renin-angiotensin system activity, has been widely demonstrated in hypertensive patients (6). Furthermore, increased urinary albumin excretion is associated with signs of subclinical organ damage, such as left ventricular hypertrophy (especially concentric geometry), and increased carotid wall thickness (7). What is even more important, microalbuminuria is a highly specific predictor of the simultaneous occurrence of

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both cardiac and vascular abnormalities. In a group of 346 patients with essential hypertension, we observed that patients with microalbuminuria actually show an almost 20-fold greater risk for having both left ventricular hypertrophy and carotid wall abnormalities (8). In light of these observations, it is not surprising that microalbuminuria was found to be an excellent predictor of cardiovascular morbidity and mortality in hypertensive patients in several prospective studies (9).

After being exposed to risk factors for variable periods of time, some patients suddenly develop acute events. However, a large number of these patients first progresses through an asymptomatic phase that is characterized by the presence of subclinical organ damage: left ventricular hypertrophy, peripheral atherosclerosis, and mild renal dysfunction (10). This asymptomatic phase often precedes and predicts the occurrence of major events. Nowadays, we can easily identify patients who are at this preclinical stage and, with appropriate aggressive multifactorial treatment, not only can prevent the occurrence of major events but also can obtain regression of organ damage. Within this context, microalbuminuria, an integrated marker of target organ damage and, therefore, of global risk, could prove to be a valuable tool in the screening and identification of hypertensive patients who are at higher cardiovascular risk thanks to its low cost and widespread availability. It is interesting that recent data from the Losartan Intervention For Endpoint study indicate that the relationship between urinary albumin excretion and cardiovascular risk holds true, well below the levels currently used to define microalbuminuria (11). Furthermore, there is evidence that the regression of left ventricular hypertrophy parallels the reduction of albuminuria and is related to it, to some degree regardless of BP changes (12). This opens the way to a broader use of microalbuminuria assessment not only for its prognostic value but also for monitoring the efficacy of treatment.

**Optimizing Target Organ Damage Evaluation in Clinical Practice**

European guidelines for hypertension (3) emphasize the importance of assessing the presence of organ damage for cardiovascular risk stratification. However, the likelihood of identifying target organ damage may vary significantly, depending on the techniques that are used (13). Noninvasive assessment of cardiac and peripheral arterial structures by ultrasonography, for example, is a reliable and an accurate way to detect left ventricular hypertrophy and/or carotid abnormalities. Accordingly, performing routine cardiovascular ultrasound scan has resulted in correctly identifying a greater number of high-risk patients. This could have important prognostic and therapeutic implications. Unfortunately, because of its relatively high cost, this procedure is not yet performed routinely, and guidelines still recommend it only in selected cases.

Conversely, an overly restrictive diagnostic approach to risk stratification could lead to significant misclassification of patients and to underestimation of their actual absolute risk with unfavorable practical and financial consequences in the long run. We previously demonstrated that the routine search for microalbuminuria, together with the use of a statistical algorithm that was developed at our department (artificial neural network), leads to the detection of a significantly higher percentage of patients with organ damage. Furthermore, it yields a stratification of risk that is almost superimposable to what is obtained by the routine use of cardiovascular ultrasonography, although at a significantly lower cost (13). Unfortunately, the usefulness of this low cost and easily obtainable test (i.e., microalbuminuria) has recently been questioned, and its use is still too often neglected in clinical practice (14). More recently, we examined the prevalence and distribution of organ damage in 405 untreated hypertensive patients and showed that microalbuminuria, left ventricular hypertrophy, and carotid abnormalities tend to cluster only in part within the same group of patients (15). Thus, one should perform all three tests (echocardiogram, ultrasound scan of carotid arteries, and microalbuminuria) on each patient to maximize the sensitivity of cardiovascular risk evaluation. Taking into consideration the differences in sensitivity and cost for each test, the diagnostic algorithm yielding the best cost-effectiveness ratio is the search for microalbuminuria, the next step is echocardiogram among the patients whose results are negative, and, last, carotid ultrasound scan.

Accurate cardiovascular risk evaluation is a prerequisite for devising cost-effective therapeutic strategies in patients with essential hypertension. In fact, the burden of risk may influence the identification of target BP and may be useful for establishing the need for specific drugs. The presence of target organ damage has an important impact on cardiovascular risk, but very much depends on the technique that is used to assess it. Furthermore, different signs of target organ damage cluster only in part; therefore, multiple, different tests should be performed on the same patients to maximize the sensitivity of the diagnostic process.

Optimizing the diagnostic approach to the detection of target organ damage is of the utmost importance for a rationale and cost-effective allocation of economic resources. Evaluation of microalbuminuria, possibly followed by ultrasound scan of cardiovascular structures, is recommended as a screening tool for target organ damage, especially in low-risk patients with essential hypertension.

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