Impact of Target Organ Damage Assessment in the Evaluation of Global Risk in Patients with Essential Hypertension

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Accurate assessment of cardiovascular risk is a key step toward optimizing the treatment of hypertensive patients. We analyzed the impact and cost-effectiveness of routine, thorough assessment of target organ damage (TOD) in evaluating risk profile in hypertension. A total of 380 never-treated patients with essential hypertension underwent routine work-up plus evaluation of albuminuria and ultrasonography of cardiac and vascular structures. The impact of these tests on risk stratification, as indicated by European Society of Hypertension-European Society of Cardiology guidelines, was assessed in light of their cost and sensitivity. The combined use of all of these tests greatly improved the detection of TOD, therefore leading to the identification of a higher percentage of patients who were at high/very high risk, as compared with those who were detected by routine clinical work-up (73% instead of 42%; \( P < 0.0001 \)). Different signs of TOD only partly cluster within the same subgroup of patients; thus, all three tests should be performed to maximize the sensitivity of the evaluation process. The diagnostic algorithm yielding the lowest cost per detected case of TOD is the search for microalbuminuria, followed by echocardiography and then carotid ultrasonography. Adopting lower cut-off values to define microalbuminuria allows us to optimize further the cost-effectiveness of diagnostic algorithms. In conclusion, because of its low cost and widespread availability, measuring albuminuria is an attractive and cost-effective screening test that is especially suitable as the first step in the large-scale diagnostic work-up of hypertensive patients.


Accurate and sensitive stratification of cardiovascular risk has an important practical impact on devising treatment strategies. In fact, the presence of a high or very high risk profile mandates immediate initiation of antihypertensive drug treatment and may be an indication for more aggressive intervention on associated risk factors and comorbidities (1,2). Furthermore, it has been proved that identifying and targeting the subset of patients who are at highest risk improves the cost-effectiveness of antihypertensive treatment, for any degree of BP reduction (3).

European Society of Hypertension-European Society of Cardiology (ESH-ESC) guidelines indicate several approaches for the evaluation of global cardiovascular risk, depending on resource availability and local know-how (1). However, the minimum work-up recommended by the guidelines is a highly insensitive approach for detecting patients with organ damage (4). In fact, it has been shown that the more extensive the diagnostic work-up, the higher the percentage of correctly identified patients at risk (5). Microalbuminuria has recently been included among the signs of target organ damage (TOD) in patients with essential hypertension, even in the absence of diabetes (1,6). Unfortunately, this test is not yet performed routinely in clinical practice, and its usefulness has recently been challenged (7), even though a growing body of evidence points to an association between this abnormality and a higher incidence of cardiovascular events (8).

Influence of Thorough Evaluation of TOD on Global Risk Profile

To assess the relative role of microalbuminuria and cardiac and vascular ultrasonography in the process of risk stratification, we compared the sensitivity and cost of these three diagnostic techniques, both alone and in various combinations, in the search for TOD in a group of 380 untreated, nondiabetic patients with essential hypertension. None of the patients had experienced previous cardiovascular and/or cerebrovascular events or presented grades III or IV hypertensive retinopathy at fundoscopy.

According to the 2003 ESH-ESC guidelines classification (1), 80 patients had grade 1 hypertension (21%), 194 had grade 2 (51%), and 106 had grade 3 (28%) hypertension. With regard to other risk factors, 44% of the patients had dyslipidemia, and 28% were smokers. Sixty-one (16%) patients had electrocardiographic signs of left ventricular hypertrophy (LVH). The prevalence of microalbuminuria, carotid thickening or plaque, and LVH at echocardiogram was 13, 32, and 49%, respectively. Overall, 232 (61%) patients showed early signs of TOD (mi-
croalbuminuria, carotid abnormalities, echo-LVH). As a result of the routine clinical work-up, 19 (5%) of the 380 patients were classified at low risk, 201 (53%) at medium, 91 (24%) at high, and the remaining 69 (18%) at very high risk. Performing one additional diagnostic test for TOD led to a substantial reclassification of risk for many patients. In fact, by measuring albuminuria, left ventricular mass index, and carotid thickness, we were able to shift 7, 17, and 22% of the patients, respectively, from low/medium to high/very high risk strata. The combined use of all of these tests led to the detection of a significantly higher percentage of patients at high/very high risk (as compared with the routine clinical screening; 73% instead of 42%; $\chi^2 = 73.6, P < 0.0001$).

Microalbuminuria is an Integrated Sign of TOD

Our data further support the role of increased urinary albumin excretion as an integrated marker of TOD. In fact, the subgroup of patients with microalbuminuria was much more likely to show either one or both of the other signs of TOD (odds ratio [OR], 20; $P < 0.0001$) as compared with patients with LVH (OR, 3; $P < 0.0001$) or carotid abnormalities (OR, 3; $P < 0.0001$). Further improvement in the cost-effectiveness of measuring albuminuria to evaluate cardiovascular risk could be obtained by adopting a cut-off value for albumin to creatinine ratio (ACR) that is lower than what is indicated by the ESH-ESC guidelines (9,10). As a matter of fact, it was shown recently that the relationship between urinary albumin excretion and cardiovascular risk holds true well below the threshold of 2.5 mg/mmol in women and 3.5 mg/mmol in men. Thus, by using a value of 1.8 mg/mmol of ACR (corresponding to the upper quintile of our study population), we were able to identify a significantly greater percentage of patients with TOD ($n = 77$ [20%] instead of $n = 49$ [13%]). A similar approach increased the sensitivity of albuminuria to 30% in detecting patients with either one or both the other signs of TOD ($P < 0.0001$, $\chi^2 = 30.27$). In fact, patients in the upper quintile of albuminuria had a six times greater risk for showing echo-LVH and/or carotid abnormalities (OR, 6.7; 95% confidence interval, 3.20 to 13.84).

Practical and Financial Implications

Because the various signs of TOD cluster only in part within the same subgroup of patients, all three tests should be performed to maximize the sensitivity of the evaluation process. Taking into account a cost of €100 per echocardiogram (11) or carotid ultrasound examination and a cost of €10 per albuminuria evaluation (mean of two determinations on different days), we calculated the cost of screening for the presence of TOD (cost = number of patients × price per examination) by various approaches (Figure 1). The actual cost per detected case of TOD

![Figure 1](http://example.com/figure1.png)

*Figure 1. Algorithm to optimize cost-effectiveness in the diagnosis of target organ damage (TOD). Mi+, patients with albuminuria $>1.8$ mmol/mol; LVH, patients with left ventricular hypertrophy (LVMI $\geq 25$ g/m² in men and $\geq 110$ g/m²); IMT+, patients with intima-media thickness $\geq 10.90$ mm, or plaque. The actual cost per detected case of TOD ($n = 127$) is expressed for each algorithm. Estimated total cost of various strategies takes into account the price of all tests performed in each sequence of tests (A1: 221 albumin tests, 184 echocardiograms, 125 carotid ultrasound (US) scans; A2: 221 albumin tests, 184 carotid US scans, 142 echocardiograms; B1: 221 echocardiograms, 137 albumin tests, 125 carotid US scans; B2: 221 echocardiograms, 137 carotid US scans, 101 albumin tests; C1: 221 carotid US scans, 153 albumin tests, 141 echocardiograms; C2: 221 carotid US scans, 153 echocardiograms, 101 albumin tests.*)
is the ratio between the cost of screening and the number of TOD cases that were identified. We chose the more rational approach of carrying out in-depth evaluation for TOD only in the subgroup of patients who were found to be at low to medium risk after minimum traditional work-up. Therefore, a considerably lower number of patients needed to be screened, resulting in a significant decrease in total cost (40%). Along these lines, the most cost-effective diagnostic algorithm is the search for microalbuminuria, followed by echocardiography, and then carotid ultrasound. Moreover, by adopting a lower cut-off value (1.8 mg/mmol) for ACR, we were able to reduce the cost per detected case by approximately 30% for albuminuria (from €84 to €59). Overall, this approach allowed for savings between €13 and €41 (i.e., 5 and 16% of the total cost of screening) for each patient we detected with TOD (Figure 1).

In conclusion, routine evaluation of risk profile can lead to underestimating the presence of TOD and, therefore, to misclassification of a substantial number of patients. Ultrasonographic evaluation of cardiac and vascular structures is a sensitive tool for detecting high-risk patients and may have a significant impact on risk profile. Thanks to its low cost and widespread availability, measuring albuminuria is an attractive and cost-effective screening test that is especially suitable as the first step in the large-scale diagnostic work-up of hypertensive patients. In the near future, the increasing prevalence of hypertension likely will not be paralleled by the availability of financial resources for primary prevention in the cardiovascular and renal field (12), and our findings therefore could have useful, practical implications for developing diagnostic-therapeutic strategies at the community level.

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