The Journal of Clinical Hypertension

WILEY

COMMENTARY OPEN ACCESS

Connecting Cardiovascular Risk Scores With Hypertensive Mediated Organ Damage

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Received: 12 August 2025 | **Revised:** 12 August 2025 | **Accepted:** 18 September 2025

Keywords: cardiovascular risk | hypertension | target organ damage

For over half a century, the scientific community has been trying to optimize the tools to classify the risk of future fatal and non-fatal cardiovascular (CV) disease in the general population as well as in different clinical settings (i.e., diabetes, hypertension, obesity). A milestone in this journey is represented by the Framingham Heart Study begun in 1948, in which factors such as age, gender, cigarette-smoking, blood cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure (BP), left ventricular hypertrophy (LVH), and diabetes mellitus have been used for the prediction of coronary artery disease (CAD) in a population-based cohort of 5573 participants (53% men) aged 30 to 74 years at baseline [1]. Estimates generated from the Framingham data showed that the 10-year incidence of CAD in a hypothetical 42-year-old adult increased progressively from 5.2% and 2.8% in men and women, respectively, with a single risk factor, to approximately 40% in both sexes with six risk factors.

Starting from the experience of the Framingham study, numerous CV risk prediction models have been developed and validated in recent decades to stratify individuals into various risk categories. The rationale behind CV risk stratification is to identify high-risk patients deserving prompt and more aggressive intervention, thus personalizing the intensity of lifestyle and risk factor management [2, 3]. In this perspective, several risk assessment tools have reached clinical relevance and have been incorporated in the current guidelines for the prevention of CV diseases.

Addressing the issue of CV risk assessment, the International and European guidelines on arterial hypertension underline that hypertension-mediated organ damage (HMOD) is a condition that identifies a high CV risk regardless of BP levels and conventional risk factors [4–6]. Consequently, these guidelines provide, through ad hoc tables and/or figures, incisive information on high CV risk conditions that include cardiac and extracardiac HMOD, warranting BP-lowering treatment. This practical approach has the merit of making the risk stratification algorithm easier and more applicable in everyday clinical practice.

Extending the landscape on the clinical significance of CV risk assessment methods, the study by Palomo-Piñón et al. [7] provides new insights into this area of research, comparing the prevalence of CV risk categories using three validated equations (Globorisk, SCORE2, and PREVENT) and assessing their association with HMOD in adult patients with hypertension. For this purpose, cross-sectional data of 4512 hypertensive patients (mean age 64 years, 61% women, BMI 28.8 kg/m^2, 38% with type 2 diabetes) from primary care enrolled in the Registry of Arterial Hypertension in Mexico were analyzed. The prevalence of CV risk categories varied widely across three risk equations, and this was also the case for their capacity to detect HMOD. The PREVENT score showed the highest median predicted 10-year CV risk (15%), followed by the Globorisk (12%) and the SCORE2 score (5.%), and, more importantly, the strongest ability to detect HMOD (AUC: 9.751, 0.735–0.750). The HMOD was defined as a composite of 6 different markers such as elevated albumin excretion (>30 mg/24 h), reduced glomerular filtration rate (eGFR <60 mL/min/1.73 m^2), aortic stiffness (pulse pressure > 60 mmHg), hypertensive retinopathy, peripheral artery disease (ABI < 0.9), left ventricular hypertrophy (LVH) (Sokolow-Lyon index > 38 mmHg or Cornell 2440 mV/sec). Using the above diagnostic criteria, 1492 patients (33%) exhibited at least one marker of HMOD. Among this subgroup of patients, the most frequent phenotype was increased aortic stiffness (52%), followed by reduced eGFR (51%), LVH (4.6%), retinopathy (2.6%),

microalbuminuria (MA; 1.9%), and peripheral artery disease (0.1%). Furthermore, 5.8% of the total HMOD was represented by "unspecified end-organ damage". Before further analyzing and discussing the results of the study, Palomo-Piñón et al. [7], we believe it is useful to focus more deeply on the diagnostic complexity and prevalence of HMOD with the aim of providing a critical reading of its potential clinical implications. The detection of asymptomatic subclinical conditions in the brain, the heart, the kidneys, central and peripheral arteries, and the eyes is of great clinical relevance because it can provide targeted therapeutic guidance on management for hypertensive individuals with low or moderate overall risk through re-classification due to the presence of HMOD. The International Society of Hypertension global hypertension practice guidelines released in 2020 recommend that serum creatinine, eGFR, dipstick urine test, and 12-lead electrocardiogram (ECG) should be performed routinely in all patients with hypertension, and further in-depth search for HMOD should be considered wherever clinically indicated and available [4]. Extended screening for HMOD, according to 2023 ESH guidelines, includes a wide array of investigations by means of ultrasound imaging (echocardiography, carotid ultrasonography), carotid-femoral (CF) or brachial-ankle pulse wave velocity (PWV), fundoscopy, ABI, coronary artery calcium scan, computed tomography, and brain magnetic resonance [5]. The extensive search for HMOD bases its rationale on the limited sensitivity and specificity of the first-line diagnostic methods routinely used for this purpose. The implementation of advanced tools, however, would require widespread availability of the procedures at a rigorous and reliable standard, which does not yet exist in all communities. Some prospective studies have provided insight into the limitations of assessing HMOD with the minimum work-up recommended by the guidelines, focusing in particular on subclinical cardiac and vascular damage.

In the APROS Study (Assessment of Prognostic Risk Observational Survey), 1074 untreated hypertensive patients classified as being of low or medium absolute cardiovascular risk using the routine diagnostic procedures, the extent of risk was reassessed by adding the results of ultrasound examinations of heart and carotid arteries [8]. The proportion of patients classified as 'low risk' decreased from 19% to 11% and those classified as "medium" risk from 81% to 36%. On the other hand, 53% of patients previously classified as "low" or "medium" risk were reclassified as "high" risk, thus suggesting that the use of ultrasound technique allows a much more accurate identification of individuals who are at high cardiovascular risk because of HMOD. A single center study conducted on a cohort of 440 patients low-risk hypertensive patients with normal ECG showed that the prevalence of LVH in this setting was rather limited (8%) and that the only predictive factor of LVH was the duration of hypertension, leading to the conclusion that echocardiographic examination should be reserved for the low-risk subset of patients who present with higher duration of hypertension [9].

Expanding the focus to a wider range of HMOD, in line with what was done by Palomo-Piñón et al. [7], the findings from a recent analysis of the Framingham Heart Study reserve particular interest [10]. The prevalence of HMOD was assessed across BP categories (normal, elevated BP, stage 1 and 2 hypertension) in 7898 individuals (mean age 52 years, 54% women,8% with type 2 diabetes) who were free of prevalent CV disease and had available measures of ECG and echocardiographic LVH, eGFR, microalbuminuria, and CFPWV. Among participants with stage 1 and stage 2 hypertension, elevated CFPWV was the most prevalent HMOD (58%), while low ABI was the least prevalent (7%). The other markers showed intermediate prevalence: carotid intima-media thickening (38%), echocardiographic LVH (30%), ECG LVH (18%), reduced kidney function (16%), and MA (15%). The above mentioned data are markedly different from those reported Palomo-Piñón et al. [7] with the unique exception of reduced renal function (16% in both populations) and, although, also increased arterial stiffness emerged as the most frequent damage phenotype in both series it should be noted that it was assessed with two different metrics (CFPWV versus a surrogate index such as pulse pressure) and found approximately 3.5 times more frequent in the Framingham population. While taking into account the demographic, clinical, and ethnic differences of the two populations, prevalence rates of ECG LVH (1.5%), MA (0.6%), retinopathy (0.8), and abnormal ABI (0.04% in the entire cohort examined by Palomo-Piñón et al. [7] were surprisingly very low. In particular, considering that diabetics in this study represented more than a third of the sample, the prevalence of MA of less than 1% appears to be completely in contrast with the vast majority of the studies that have addressed this issue in patients with hypertension of varying severity, burden of comorbidities, and different ethnicities. Indeed, a consistent body of evidence reports that the prevalence of MA in the setting of hypertension can vary widely between 5% and 50% depending on the clinical characteristics and diagnostic methods used [11, 12]. This also applies to LVH, retinopathy, and peripheral artery disease [13, 14]. Furthermore, it should be mentioned that the inclusion of "unspecified end-organ damage" in the composite HMOD, as well as the possibility of classifying a marker on the basis of "self-reported outcome," would not appear to reflect a rigorous and reliable classification method in revealing subclinical cardiac and vascular alterations. Keeping these limitations in mind, the HMOD landscape in this Mexican hypertensive population is quite nuanced and somewhat distorted in some key parameters. Finally, the head-to-head comparison of the three algorithms provides information on the greater predictive accuracy of PREVENT compared to Globorisk and SCORE 2; however, it should be noted that only PREVENT incorporates a measure of organ damage, such as eGFR, and this may itself represent a confounder in this type of analysis [15]. Nevertheless, the study by Palomo-Piñón et al. [7] has the undoubted merit of exploring the relationship between individual total CV risk, assessed by validated algorithms, and the likelihood of having HMOD, stimulating the debate on a crucial topic in preventive medicine. While it would be desirable for every hypertensive patient worldwide to have a minimum HMOD work-up, in accordance with the guidelines, in more depth research into HMOD, beyond the clinical reasons, should take into account the overall risk profile.

Conflicts of Interest

The authors report no conflicts of interest.

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