Risk stratification in hypertension: NT-proBNP and R wave in aVL lead combination better than echocardiographic left ventricular mass

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Objectives: Plasma N-terminal pro brain natriuretic peptide (NT-proBNP) and R wave in aVL lead (RaVL) have been associated with mortality in hypertension. The aim of the current study was to compare the prognostic value of their combination to that of the left ventricular mass index (LVMI) assessed by echocardiography.

Methods: A total of 1104 hypertensive patients who had at baseline an assessment of plasma NT-proBNP, a 12-lead ECG, and echocardiography were included. LVMI was assessable in 921 patients. After a median (interquartile range) follow-up of 8.5 (5.4–13.3) years, 110 deaths occurred, 62 of which were from a cardiovascular cause.

Results: Optimal thresholds of RaVL and plasma NT-proBNP to predict mortality were 0.7 mV and 150 pg/ml, respectively. A three-modality variable based on RaVL and NT-proBNP was built: 0 when none were above the threshold, 1 or 2 when only one or both were above the threshold. After adjustment for all confounders including LVMI indexed to height raised to the allometric power of 2.7 in Cox regression analysis, we observed a significant increased risk for patients having one marker above the threshold for all-cause and cardiovascular mortality [hazard ratio: 1.76; 95% confidence interval (1.08–2.86); 2.18 (1.06–4.46)] and for those having two markers above the threshold [2.76 (1.51–5.03); 3.90 (1.69–9.00)]. The prognostic value of the combination had the highest C-index (0.772 and 0.839, respectively) in comparison with LVMI (0.746 and 0.806, respectively).

Conclusion: Risk stratification in hypertension using the combination of NT-proBNP and RaVL is a simple method that may be considered in first line screening.

Keywords: ECG, echocardiography, hypertension, left ventricular hypertrophy, mortality, NT-proBNP

Abbreviations: ABPM, ambulatory blood pressure monitoring; ComboR-NT-pro, variable combining RaVL and NT-proBNP; eGFR, estimated glomerular filtration rate; GP, general practitioner; HMOD, hypertensive-mediated organ damage; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro brain natriuretic peptide; PWV, pulse wave velocity; RaVL, R wave in aVL lead; TTE, transthoracic echocardiography

Risk stratification is a key issue in the management of hypertension. It is largely based on the detection of hypertensive-mediated organ damage (HMOD) subclinical target organ damage [1], the number of which gradually increases cardiovascular risk [2,3]. Cardiac screening is of particular importance as emphasized by the WHO [4], and the routine gold-standard test is echocardiography, which allows the detection of left ventricular (LV) hypertrophy (LVH), an extensively reported prognostic factor [5,6]. However, not every hypertensive patient will undergo transthoracic echocardiography (TTE) owing to cost and insufficient availability; furthermore, the accuracy of this method suffers from important limitations [5,7,8]. More generally, risk stratification in hypertension is primarily the task of general practitioners (GPs), but is poorly executed [9], probably because of complexity and/or local facilities. For cardiac assessment, specifically, two parameters that are simpler to measure may also be used, the first of which is a 12-lead ECG, and namely the R wave in aVL lead (RaVL). RaVL has been shown to be tightly correlated with LV mass index (LVMI) [10–12], but ECG indices usually suffer from insufficient sensitivity [12,13], which limits their value in mild-to-moderate hypertension. Plasma N-terminal pro brain natriuretic peptide (NT-proBNP) has been proposed as another powerful marker of LVH [10,12,14] and has the advantage of being integrative, encompassing hypertension severity [15], aortic stiffening, renal, and heart failures [16]. In addition to being easily available, RaVL and plasma NT-proBNP have a major prognostic significance in hypertension [11,17,18], even in patients without heart failure [19].

Journal of Hypertension 2020, 38:65–72

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Received 10 June 2019 **Revised** 28 July 2019 **Accepted** 30 July 2019
DOI:10.1097/HJH.0000000000002225

It has been shown that the combination of NT-proBNP and RaVL worked better than echocardiography for categorizing LVH in comparison with MRI [10]. We hypothesized that the combination of NT-proBNP and RaVL could be more efficient than echocardiography for risk stratification in hypertensive patients. Thus, the main objective of the current study was to compare the prognostic value of the combination of RaVL and plasma NT-proBNP with that of echocardiographic LVH on all-cause and cardiovascular mortality in hypertension (ClinicalTrials.gov Identifier: NCT03068364).

PATIENTS AND METHODS

Our ongoing hypertensive cohort includes 1611 patients who had a hypertension work-up in the cardiology department of Croix-Rousse hospital (Hospices Civils de Lyon, Lyon, France) from January 1997 to January 2014. Adult patients (≥18 years) were included in this cohort provided that they agreed to have their data collected (part of this cohort has been previously published [19]). The study was approved by the Ethics Committee and an informed consent was obtained from every patient. NT-proBNP was routinely measured in this cohort since 1998. To be included in the current study, patients had to have a NT-proBNP measurement, an ECG, and echocardiography; patients lost to follow-up were excluded. A total of 1104 patients fulfilled these criteria and were included (Fig. S1, http://links.lww.com/HJH/B138). Of note, patients excluded from the cohort had very similar characteristics in comparison with those included (data not shown).

Baseline work-up

The baseline workup and heart failure definition have been described previously [16] and is detailed in the supplementary data.

A 12-lead ECG was performed in the supine position to measure R wave in aVL lead. Two-dimensional images, M-mode, and Doppler recordings were obtained from a Vivid 5 or e9 ultrasound device (GE Vingmed Ultrasound, Horten, Norway). The thickness of the interventricular septum (IVS), that of the posterior wall, and the diameter of the LV (LVD) were assessed according to the Penn convention [20]. Each parameter was recorded over three consecutive heartbeats ignoring other data. The LV dimensions were determined from M-mode images and used to calculate LV mass (LVM) with the Devereux formula: $LVM = 1.04[(IVS + LVD + PW)^3 - LVD^3] - 13.6$. The LVMI was defined in two different ways: first, indexation to the BSA (TTE $LVMI^{BSA}$) according to the European Society of Cardiology – European Society of Hypertension guidelines with the following LVH criteria: TTE $LVMI^{BSA}$ more than 115 g/m^2 in men and more than 95 g/m^2 in women; and second, indexation to height (in meters) raised to the allometric power of 2.7 (TTE $LVMI^{2.7}$) with the following LVH criterion: TTE $LVMI^{2.7}$ more than 51 $g/m^{2.7}$ in both sexes [1]. Patients with LVMI not measurable because images that were not perpendicular to the LV axis or with poor echogenicity were considered in the current study as having unassessable LVMI.

The renal function was assessed using the modification of diet in renal disease formula. Plasma NT-proBNP concentration was assessed at the end of the night-time period using an ELISA kit (Roche Diagnostics, Meylan, France; range lower limit of detection: 5 pg/ml, upper limit of quantification: 35 000 pg/ml).

Assessment of outcomes

Vital status was obtained by the INSEE CépiDC unit in July 2016. The endpoints used in this study were all-cause death (cardiovascular and noncardiovascular death) and cardiovascular death (from cerebrovascular disease, myocardial infarction, heart failure, renal death, and sudden death).

Statistical analysis

Variables were summarized as mean ± SD, except those with a skewed distribution, expressed as median [interquartile range (IQR)] and categorical variables expressed as percentages. Analysis of variance (ANOVA) or nonparametric ANOVA was used to compare continuous variables, and the χ^2 test was used for comparisons of dichotomous variables.

A variable combining RaVL and NT-proBNP (ComboR-NT-pro) was built as follows: 0 = both RaVL and NT-proBNP below thresholds (reference value), 1 = either RaVL or NT-proBNP above thresholds, 2 = both RaVL and NT-proBNP above thresholds. The thresholds for RaVL and plasma NT-proBNP to predict all-cause and cardiovascular death were screened using Harrell's C-index [21] and cubic splines. The C-index is defined as the proportion of patients in whom the predictions and outcomes are concordant. The optimal cutoff values were identified from the highest value of C-index and from cubic splines (the first value with hazard ratio more than 1.5 and significant confidence interval).

The prognostic value of ComboR-NT-pro, TTE $LVMI^{BSA}$, and TTE $LVMI^{2.7}$ were analyzed first by Kaplan–Meier curves (Log-rank test) according to an optimal threshold (RaVL, plasma NT-proBNP, and ComboR-NT-pro) or recommended value (TTE $LVMI^{BSA}$, TTE $LVMI^{2.7}$). Univariate and multivariable Cox regression analyses were performed to assess their predictive values. Two subtypes of multivariable Cox regression models were tested. The first subtype was built on the basis of an adjustment on age, sex, daytime systolic ambulatory blood pressure (BP) measurement (ABPM), and either: ComboR-NT-pro (0,1,2) and TTE $LVMI^{2.7}$ (three-modality variable, LVH no, yes, unassessable) (Model 1A); ComboR-NT-pro (0,1,2) and TTE $LVMI^{BSA}$ (LVH no, yes, unassessable) (Model 1B); ComboR-NT-pro (0,1,2) and TTE $LVMI^{2.7}$ (continuous variable) (Model 1C); ComboR-NT-pro (0,1,2) and TTE $LVMI^{BSA}$ (continuous variable) (Model 1D). The second subtype was built on the basis of an adjustment on age, sex, systolic ABPM, smoking status, diabetes, LDL cholesterol, estimated glomerular filtration rate (eGFR), BMI, previous cardiovascular event (stroke, heart failure, peripheral artery disease, coronary artery disease), and number of antihypertensive treatments, and either: ComboR-NT-pro (0,1,2) and TTE $LVMI^{2.7}$ (LVH no, yes, unassessable) (Model 2A); ComboR-NT-pro (0,1,2) and TTE $LVMI^{BSA}$ (LVH no, yes, unassessable) (Model 2B); ComboR-NT-pro (0,1,2) and TTE $LVMI^{2.7}$ (continuous variable) (Model 2C); ComboR-NT-pro (0,1,2) and TTE $LVMI^{BSA}$ (continuous variable) (Model 2D). Sensitivity analyses were performed excluding patients without

assessment of LVMI (Models 2A and 2B, not for models 2C and 2D because patients were previously excluded in the absence of continuous variable available) or with a previous history of heart failure (Models 2A, 2B, 2C, 2D). All variables-by-time interactions were tested in this model to confirm the hypothesis of proportional hazards. No statistically time interaction regarding all-cause or cardiovascular death was found.

To estimate the increased discriminative prognostic value of each biomarker, we built different multivariable Cox models starting with Model 2 (no biomarkers). In the first step, we add in turn ComboR-NT-pro, TTE $LVMI^{BSA}$, or TTE $LVMI^{2.7}$ in the model. In the second step we add biomarkers that were not used in the first step. The predictive accuracy was determined by Harrell's C-index [21]. In addition, to test the information gain in predicting the outcome by adding biomarkers, different multivariable models that included ComboR-NT-pro, and LV mass were compared with the model that excluded all of them using the likelihood ratio test.

The analyses were performed using SPSS v20.0.0 (SPSS, Chicago, Illinois, USA) and STATA 12 (Stata Corporation, College Station, Texas, USA). A P value less than 0.05 was considered for statistical significance.

RESULTS

Baseline characteristics

Briefly, half the cohort were men (51.6%) and the mean age was 50.5 years (Table 1). There were 821 patients treated by at least one antihypertensive drug; 934 patients had uncontrolled daytime ambulatory BP (systolic >135 mmHg and/or diastolic >85 mmHg). With respect to causes, 941 patients had essential hypertension (85.2%); the other causes were primary aldosteronism (12.1%), renal artery stenosis (1.4%), renal parenchymal disease (0.3%), and pheochromocytoma (0.8%). At baseline, patients were treated with the following medication: calcium channel blockers (57.4%, $n=634$), alpha-blockers (35.3%, $n=390$), centrally acting drugs (15.9%, $n=176$), beta-blockers (9.3%, $n=103$), angiotensin II receptor blockers (6.2%, $n=68$), thiazide diuretics (4.7%, $n=52$), angiotensin-converting enzyme inhibitors (3.5%, $n=39$), furosemide (3.5%, $n=39$), spironolactone (2.4%, $n=27$), and amiloride (0.5%, $n=6$). Among the 1104 included patients, 921 (83.4%) had their LVM measured; 183 patients (16.6%) had unassessable LVM for technical reasons.

Biomarker thresholds

After a median (IQR) follow-up of 8.5 (5.4–13.3) years, there were 110 deaths, 62 of which were from a cardiovascular cause. Using C-index and cubic splines, the optimal thresholds associated with RaVL were 0.7 mV for both cardiovascular and all-cause mortality. The thresholds associated with plasma NT-proBNP were 150 for cardiovascular, and 150 pg/ml for all-cause mortality (Figs. S2 and S3, http://links.lww.com/HJH/B138). When stratified according to RaVL and NT-proBNP separately, patients above these thresholds had a significantly worse cardiovascular risk profile: older age, higher median SBP, had more frequently diabetes, coronary artery disease, and stroke, lower eGFR (Table S1, http://links.lww.com/HJH/B138). When stratified according to ComboR-NT-pro, an increase of cardiovascular risk profile was observed in function of this score (Table 1).

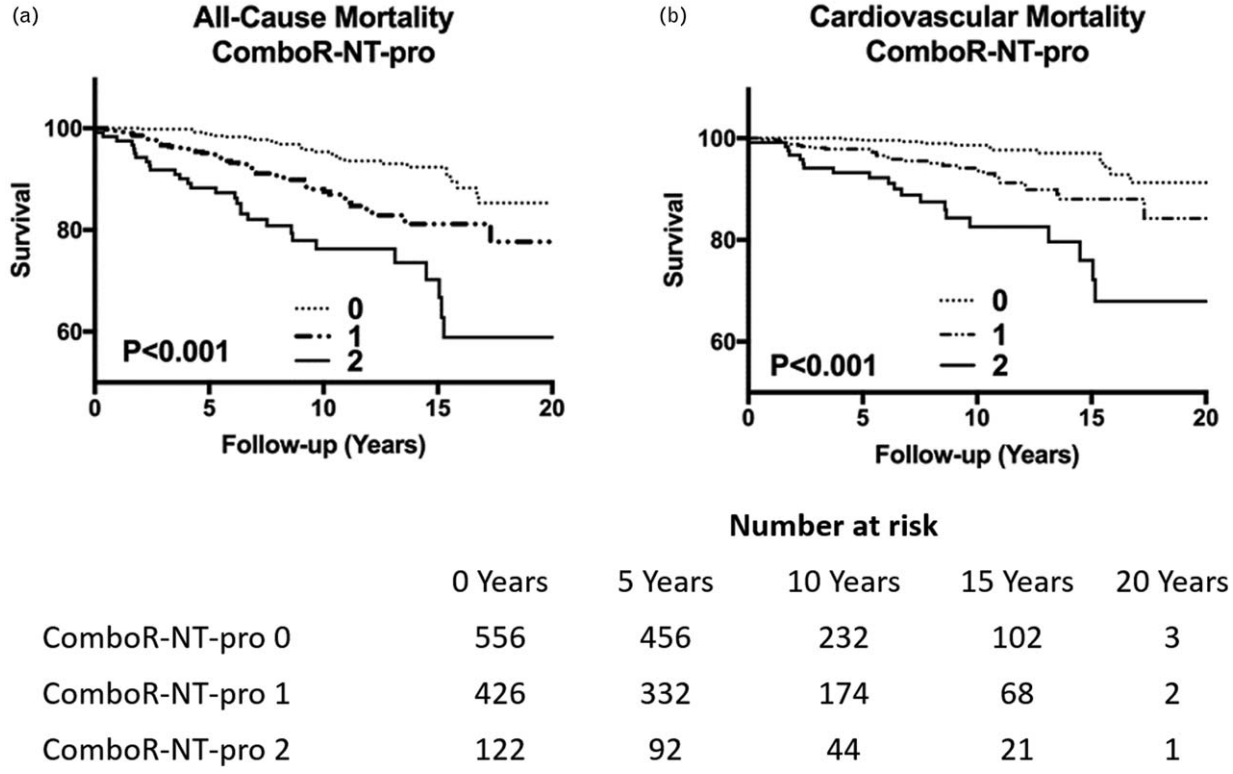
Survival analysis

Kaplan–Meier analysis found that the survival of patients with ComboR-NT-pro at least 1 was significantly worse than those with a ComboR-NT-pro at 0 (Log-rank: all $P \leq 0.001$; Fig. 1). Similarly both echocardiographic LVH indexes were

TABLE 1. Baseline characteristics of the total cohort and according to variable combining R wave in aVL lead and NT-proBNP

	Total cohort, $n=1104$	ComboR-NT-pro = 0, $n=556$	ComboR-NT-pro = 1, $n=426$	ComboR-NT-pro = 2, $n=122$	P value
Demographic characteristics					
Mean age (years)	50.5 ± 14.7	45.8 ± 13.9	54.2 ± 13.8	59.4 ± 13.3	<0.001
Women/Men (%)	48.4/51.6	50.0/50.0	46.5/53.5	47.5/52.5	0.539
BMI (kg/m^2)	26.2 (23.4–29.4)	25.7 (22.7–28.9)	27.0 (24.4–29.7)	27.8 (25.0–31.5)	<0.001
Daytime SBP (mmHg)	153 (140–165)	147 (137–157)	154 (144–169)	168 (154–184)	<0.001
Daytime DBP (mmHg)	92 (84–101)	92 (83–99)	92 (84–102)	95 (84–108)	0.060
Medical history					
Current smoking (%)	19.9	20.5	19.5	18.9	0.880
Diabetes (%)	13.0	8.8	15.0	25.4	<0.001
Heart failure (%)	4.7	2.9	5.2	11.5	<0.001
Stroke (%)	5.4	2.9	6.1	9.8	0.002
Coronary artery disease (%)	4.9	2.0	8.2	11.5	<0.001
Renal and cardiac assessment					
NT-proBNP (pg/ml)	76 (37–167)	49 (28–82)	121 (48–254)	310 (203–614)	<0.001
RaVL (mV)	6 (3–9)	4 (2–6)	8 (5–10)	11 (9–13)	<0.001
eGFR (ml/min)	87.3 ± 23.4	92.1 ± 21.5	85.2 ± 23.5	72.0 ± 24.6	<0.001
TTE $LVMI^{BSA}$ (g/m^2)	113.5 (88.6–144.5)	96.9 (79.1–124.0)	124.9 (101.6–156.9)	164.0 (120.9–203.7)	<0.001
TTE $LVMI^{2.7}$ (g/m$^{2.7}$)	52.7 (40.8–63.6)	46.5 (35.7–59.6)	60.8 (48.7–69.3)	68.0 (54.0–91.2)	<0.001
LDL cholesterol (mmol/l)	3.1 ± 0.9	3.1 ± 0.9	3.2 ± 0.9	3.1 ± 1.1	0.538
Antihypertensive treatment, n	1.4 ± 1.1	1.1 ± 1.0	1.5 ± 1.1	2.2 ± 1.3	<0.001

Unless otherwise stated, the data are mean ± SD or median (interquartile range). ComboR-NT-pro variable: 0 = both RaVL AND NT-proBNP below thresholds (reference value), 1 = either RaVL or NT-proBNP above thresholds, 2 = both RaVL and NT-proBNP above thresholds. eGFR, estimated glomerular filtration rate; $LVMI^{2.7}$, left ventricular mass indexed to height to the allometric power of 2.7; $LVMI^{BSA}$, left ventricular mass indexed to BSA; NT-proBNP, N-terminal pro brain natriuretic peptide; TTE, transthoracic echocardiography.



Number at risk

	0 Years	5 Years	10 Years	15 Years	20 Years
ComboR-NT-pro 0	556	456	232	102	3
ComboR-NT-pro 1	426	332	174	68	2
ComboR-NT-pro 2	122	92	44	21	1

FIGURE 1 Kaplan–Meier survival curves relative to optimal thresholds of variable combining R wave in aVL lead and NT-proBNP (panels a and b). Variable combining R wave in aVL lead and NT-proBNP is based on the combination of NT-proBNP and R wave in aVL; 0, 1, 2 denote the number of constitutive variables above the threshold. NT-proBNP, N-terminal pro brain natriuretic peptide.

predictors of all-cause and cardiovascular death in the subset of patients with LVMI available ($n = 921$; Fig. 2).

Univariate Cox regression analyses found a worsening of outcome in function of increasing ComboR-NT-pro level. Similarly, in univariate analysis, both TTE $LVMI^{2.7}$ and TTE $LVMI^{BSA}$ were predictors of all-cause and cardiovascular mortality (Table S2, http://links.lww.com/HJH/B138). After adjustment on age, sex and daytime systolic ABPM (Models 1A–D), the two levels of ComboR-NT-pro remained significantly associated with all-cause and cardiovascular mortality, except for Model 1D in which we observed only a trend for cardiovascular mortality (Table 2). Conversely, TTE $LVMI^{2.7}$ and TTE $LVMI^{BSA}$, considered either as a categorical or continuous variable, were not associated with either endpoint in all subtypes of models 1 (Table 2). After adjustment on all cardiovascular risk factors, antihypertensive treatment and previous cardiovascular events (Models 2A–D), ComboR-NT-pro at two points was still significantly associated with all-cause and cardiovascular mortality, except for model 2D in which we only observed a trend (Table 3). Conversely, TTE $LVMI^{2.7}$ and TTE $LVMI^{BSA}$, considered either as a categorical or continuous variable, were not associated with either endpoint in all subtypes of model 2 (Table 3). Similar results were found for the ComboR-NT-pro variable in a sensitivity analysis excluding patients with a previous history or current symptoms of heart failure (Models 2A–D; $n = 1052$; Table S3, http://links.lww.com/HJH/B138) or patients with previous cardiovascular events (stroke, heart failure and coronary artery disease, Models 2A–D; $n = 960$; Table S4, http://links.lww.com/HJH/B138).

When ComboR-NT-pro was associated together with LVMI in multivariable models 2A and 2B, ComboR-NT-pro was significantly associated with both all-cause and cardiovascular mortality but not TTE $LVMI^{2.7}$ in the subset of patients with LVMI available ($n = 917$; Table S5, http://links.lww.com/HJH/B138).

The additional value of ComboR-NT-pro, TTE $LVMI^{2.7}$, and TTE $LVMI^{BSA}$ was tested using C-index and the likelihood ratio test in multivariable Model 2. Overall, the highest C-index and likelihood ratio test were observed for ComboR-NT-pro for cardiovascular (Fig. 3) and all-cause mortality (Fig. S4, http://links.lww.com/HJH/B138).

DISCUSSION

The current study found that the combination of RaVL and plasma NT-proBNP is a prognostic marker of mortality in hypertensive patients, and this combination appeared superior to echocardiography. These results advocate for a change of practice by implementing in routine this simple and probably cost-effective approach to stratify the risk of hypertensive patients.

The current study shows that considering ComboR-NT-pro (the combination of RaVL and NT-proBNP) is a better prognostic marker than two well-acknowledged LVMI measurements (TTE $LVMI^{2.7}$ and TTE $LVMI^{BSA}$). This could be explained, on the one hand, by the additive performance of two powerful biomarkers and, on the other hand, by weaknesses of echocardiography to assess LVMI. With respect to the first point, both RaVL and NT-proBNP have been found to be associated with cardiac remodeling

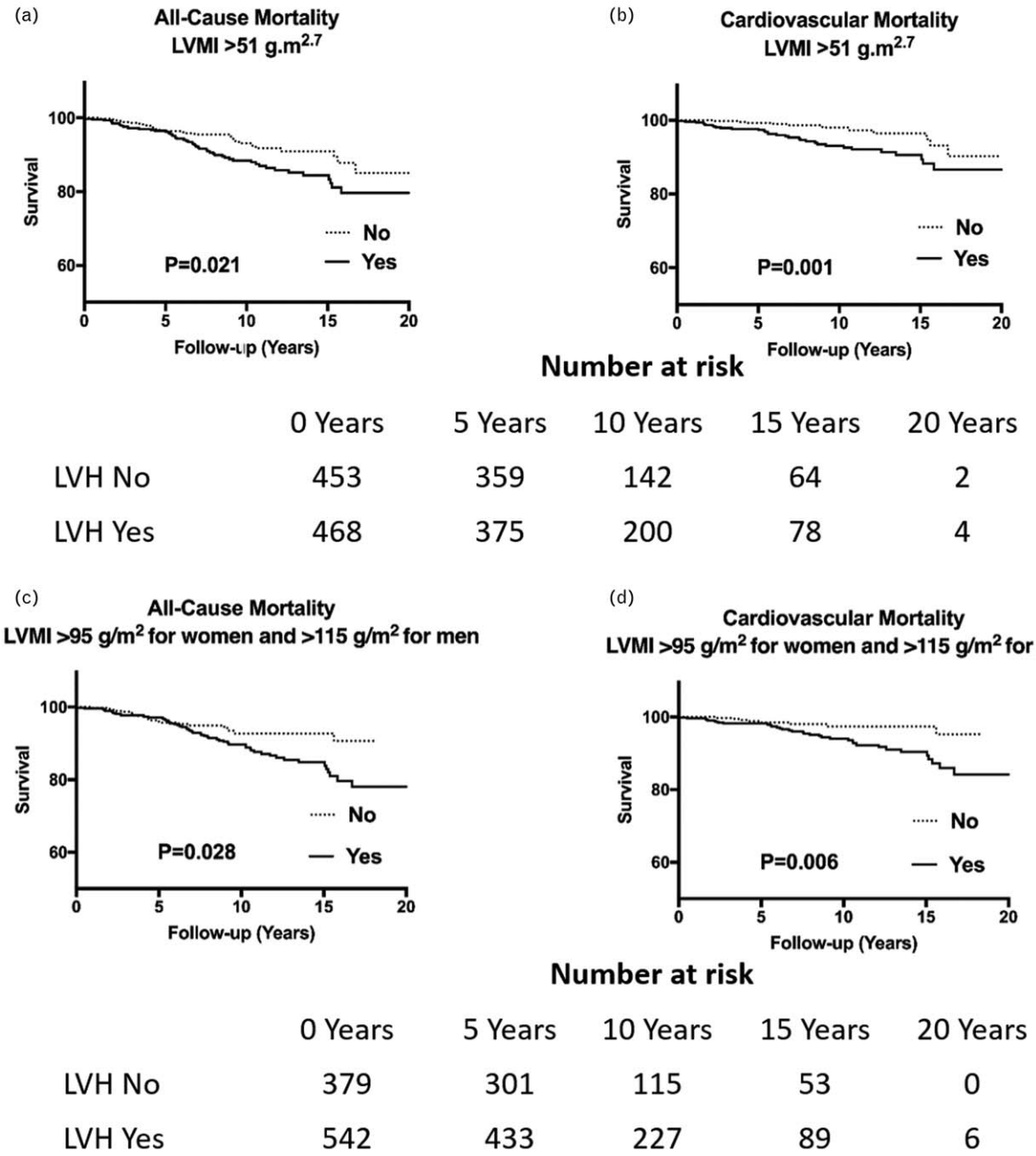


FIGURE 2 Kaplan–Meier curves relative to the status of left ventricular hypertrophy according to left ventricular mass indexed to height to the allometric power of 2.7 (panels a and b) and indexed to BSA (panels c and d).

[10,22,23], and LVH is particularly relevant in hypertension because it has demonstrated strong prognostic value [5,6]. Furthermore, it is of note that the combination of RaVL and NT-proBNP leads to the diagnosis of LVH assessed by MRI with a performance similar to that of echocardiography [10]. In keeping with this result, the current study found a gradual increase of LVMI, irrespective of the indexation method, with ComboR-NT-pro value. In addition, NT-proBNP is also associated with other important HMOD, namely eGFR and carotid–femoral pulse wave velocity (PWV) [16]; again, data from the current study regarding renal function and BP confirm this previous report. The strong prognostic value of PWV [24,25] and its association with plasma NT-proBNP [16] may explain the predictive value of the latter. Moreover, the association between plasma NT-proBNP and mortality persist even after exclusion of patients with history or current symptoms of heart failure. The level of the biomarker may also be augmented by a subtle increase of LV filling pressure thus allowing the detection of a high-risk population prone to develop heart failure [26]. It is also of note that the optimal cutoff at 150 pg/ml to predict mortality was similar to that estimated in the first appraisal of this cohort almost ten years ago, 133 pg/ml [19], and also to the 131 pg/ml threshold proposed to detect damage of at least one HMOD [16].

TABLE 2. Multivariable Cox regression survival analyses subtype 1 adjusted on age, sex, and daytime SBP

		All-cause mortality		Cardiovascular mortality	
	n	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Multivariable 1A	1104				
TTE $LVMI^{2.7}$ no LVH (reference)		–	–	–	–
TTE $LVMI^{2.7}$ LVH		1.04 (0.62–1.74)	0.892	1.32 (0.62–2.83)	0.471
TTE $LVMI^{2.7}$ not assessed		1.32 (0.75–2.32)	0.330	1.68 (0.75–3.80)	0.210
ComboR-NT-pro (0)		–	–	–	–
ComboR-NT-pro (1)		1.96 (1.21–3.15)	0.006	2.51 (1.25–5.05)	0.010
ComboR-NT-pro (2)		3.57 (2.01–6.36)	<0.001	5.20 (2.35–11.50)	<0.001
Multivariable 1B	1104				
TTE $LVMI^{BSA}$ no LVH		–	–	–	–
TTE $LVMI^{BSA}$		0.93 (0.55–1.58)	0.787	1.70 (0.64–4.54)	0.290
TTE $LVMI^{BSA}$ not assessed		1.28 (0.72–2.29)	0.406	2.47 (0.88–6.96)	0.086
ComboR-NT-pro (0)		–	–	–	–
ComboR-NT-pro (1)		1.99 (1.24–3.20)	0.005	2.88 (1.33–6.27)	0.008
ComboR-NT-pro (2)		3.67 (2.08–6.48)	<0.001	4.82 (1.99–11.70)	<0.001
Multivariable 1C	917				
LVMI (+10 $g/m^{2.7}$)		1.02 (0.93–1.12)	0.647	1.04 (0.92–1.18)	0.513
ComboR-NT-pro (0)		–	–	–	–
ComboR-NT-pro (1)		1.95 (1.21–3.14)	0.006	3.01 (1.38–6.58)	0.006
ComboR-NT-pro (2)		3.47 (1.92–6.23)	<0.001	4.84 (1.92–12.19)	0.001
Multivariable 1D	917				
LVMI (+10 g/m^2)		1.03 (0.98–1.07)	0.316	1.04 (0.98–1.11)	0.206
ComboR-NT-pro (0)		–	–	–	–
ComboR-NT-pro (1)		1.83 (1.06–3.18)	0.031	2.34 (0.98–5.58)	0.054
ComboR-NT-pro (2)		2.72 (1.34–5.55)	0.006	2.74 (0.91–8.26)	0.073

ComboR-NT-pro: 0 = both RaVL AND NT-proBNP below thresholds (reference value), 1 = either RaVL or NT-proBNP above thresholds, 2 = both RaVL and NT-proBNP above thresholds.
CI, confidence interval; HR, hazard ratio; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro brain natriuretic peptide; TTE, transthoracic echocardiography.

Regarding RaVL, the proposed threshold at 0.7 mV is in good agreement with other values previously reported to predict mortality [18] or cardiovascular events [11,17]. However, herein, RaVL was less strongly associated with mortality than that found in the historical OLD-HTA cohort [18]. This difference may be explained by a reduction of all-cause mortality during the past decade and by the development of more effective antihypertensive treatments

TABLE 3. Multivariable Cox regression survival analyses subtype 2 adjusted on age, sex, daytime SBP, smoking status, diabetes, LDL cholesterol, estimated glomerular filtration rate, BMI, previous cardiovascular event, and antihypertensive treatment

		All-cause mortality		Cardiovascular mortality	
	n	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Multivariable 2A	1104				
TTE $LVMI^{2.7}$ no LVH (reference)		–	–	–	–
TTE $LVMI^{2.7}$ LVH		0.91 (0.53–1.57)	0.907	1.17 (0.53–2.59)	0.702
TTE $LVMI^{2.7}$ not assessed		1.21 (0.68–2.18)	0.517	1.59 (0.68–3.70)	0.286
ComboR-NT-pro (0)		–	–	–	–
ComboR-NT-pro (1)		1.76 (1.08–2.86)	0.023	2.18 (1.06–4.46)	0.033
ComboR-NT-pro (2)		2.76 (1.51–5.03)	0.001	3.90 (1.69–9.00)	0.001
Multivariable 2B	1104				
TTE $LVMI^{BSA}$ no LVH		–	–	–	–
TTE $LVMI^{BSA}$		0.81 (0.47–1.40)	0.439	1.45 (0.53–3.93)	0.470
TTE $LVMI^{BSA}$ not assessed		1.14 (0.62–2.09)	0.675	2.12 (0.73–6.15)	0.168
ComboR-NT-pro (0)		–	–	–	–
ComboR-NT-pro (1)		1.77 (1.08–2.90)	0.023	2.50 (1.13–5.52)	0.024
ComboR-NT-pro (2)		2.59 (1.41–4.77)	0.002	3.22 (1.26–8.23)	0.015
Multivariable 2C	917				
LVMI (+10 $g/m^{2.7}$)		1.00 (0.90–1.11)	0.994	0.99 (0.87–1.14)	0.936
ComboR-NT-pro (0)		–	–	–	–
ComboR-NT-pro (1)		1.74 (1.07–2.84)	0.027	2.69 (1.22–5.94)	0.014
ComboR-NT-pro (2)		2.52 (1.35–4.70)	0.004	3.42 (1.32–8.88)	0.012
Multivariable 2D	917				
LVMI (+10 g/m^2)		1.01 (0.96–1.06)	0.759	1.02 (0.95–1.10)	0.518
ComboR-NT-pro (0)		–	–	–	–
ComboR-NT-pro (1)		1.77 (1.01–3.10)	0.046	1.74 (0.55–5.53)	0.351
ComboR-NT-pro (2)		1.89 (0.89–4.04)	0.100	2.20 (0.92–5.25)	0.076

ComboR-NT-pro: 0 = both RaVL AND NT-proBNP below thresholds (reference value), 1 = either RaVL or NT-proBNP above thresholds, 2 = both RaVL and NT-proBNP above thresholds.
CI, confidence interval; HR, hazard ratio; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro brain natriuretic peptide; TTE, transthoracic echocardiography.

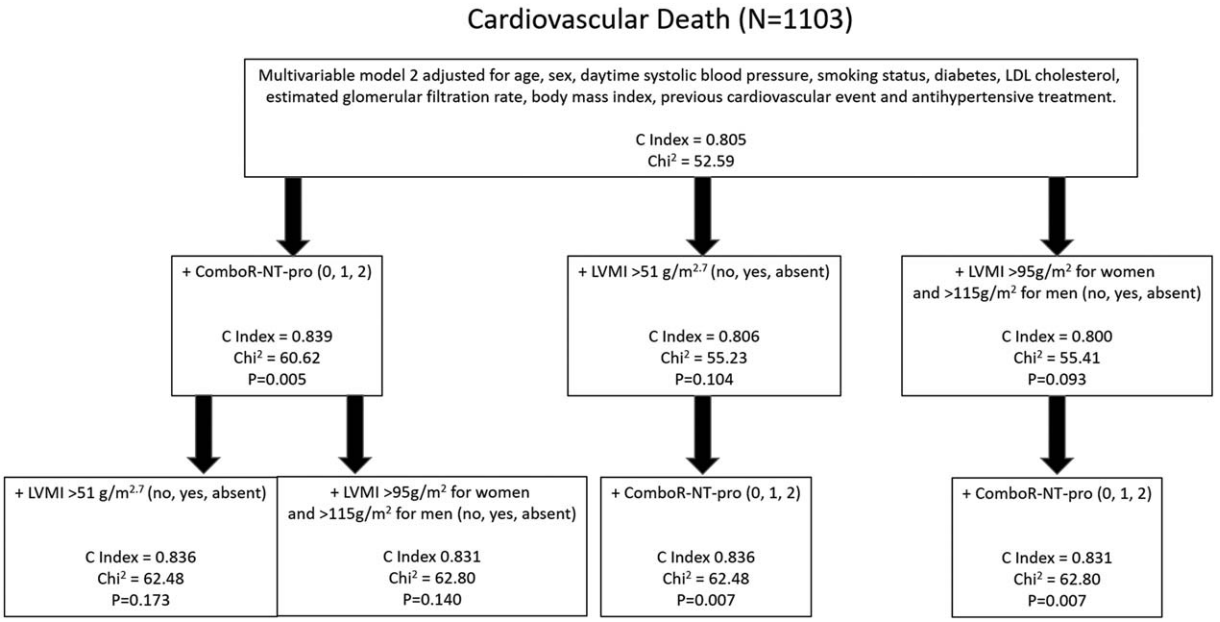


FIGURE 3 Predictive accuracy and information gain for variable combining R wave in aVL lead and NT-proBNP, and left ventricular mass index for cardiovascular mortality. NT-proBNP, N-terminal pro brain natriuretic peptide.

(angiotensin II receptor blocker, angiotensin-converting enzyme inhibitor, and calcium channels blockers) particularly in the presence of LVH [27]. Nevertheless, it is ComboR-NT-pro (the combination of both RaVL and NT-proBNP) that yields the best results, as assessed by the C-index approach, although the predictive gain provided by RaVL over NT-proBNP seems limited. In multivariable analysis, patients having a ComboR-NT-pro at 2 defined a high-risk subgroup of patients with a nearly four-fold increased risk of cardiovascular death, and those with ComboR-NT-pro at 1 had a two-fold increased risk of cardiovascular mortality (without significant difference between the two levels); similar results were observed for all-cause mortality but the associations were weaker. This suggests that the prognostic information provided by the two biomarkers is not strictly superimposable. It may be explained by the stronger correlation between NT-proBNP and anatomical (TTE LVMI) than electrical LVH (ECG) [16] that reflect different pathophysiological mechanisms: myocyte hypertrophy and interstitial remodeling for the former, and ion channel remodeling for the latter [28]. This is further supported by epidemiological data demonstrating independent effects on cardiovascular events [29–31].

Although TTE does provide a great deal of information (systolic and diastolic function, valvular assessment, ascending aorta diameter...) [12], there are several limits for its application to the evaluation of LVMI among which are an overestimation of LVM, poor reproducibility, and unavailability of results in more than 10% of hypertensive patients for technical reasons [5,7,8]. For instance, more than 16% of patients herein did not have LVMI assessment for technical reasons, despite a strict method of measurement and trained operators. In comparison, RaVL and NT-proBNP are highly reproducible, which may contribute to their predictive performance [11,16,18]. Furthermore, the high cost and limited availability of echocardiography with regard to the number of hypertensive patients makes the ComboR-NT-pro approach very tempting as a first screening step. In this strategy, echocardiography would be proposed to patients with a ComboR-NT-pro at 1 or 2 and, of course, to patients with clinical abnormalities or symptoms. This would rationalize the need for echocardiography and allow GPs to manage hypertensive patients with user-friendly tools.

Limits

The current study was performed in a tertiary healthcare institution and most patients were treated at baseline with antihypertensive treatment that did not interfere with hormonal regulation; this might have reduced the generalizability of the results for a first screening in untreated patients or those with drugs interfering with hormone regulation [32]. However, the baseline characteristics of this population indicated a fairly low-risk profile. We, therefore, believe that the patients included in the current study may be well taken as everyday hypertensive patients. Moreover, residual confounding due unmeasured bias might exist despite the adjustment performed (frequency of visits, achievement of BP control and incidence of other risk factors during follow-up). However, it is unlikely that excluded patients with missing data at baseline may influence our results because they had very similar characteristics compared those included in the current study. On the other hand, the rather poor performance of echocardiography cannot be attributed to this setting since, conversely, echocardiography was performed following a very strict protocol, and it is likely that the performance of echocardiography in a real-life setting would be even worse for assessing LVMI. Finally, we used PENN convention to assess LVMI as it was the recommended method at the beginning of the cohort; this PENN convention was used all along the inclusion period to provide homogeneous data.

Perspectives

The results show that a ComboR-NT-pro strategy based on the combination of NT-proBNP and RaVL with respective

thresholds at 150 pg/ml and 0.7 mV seems adequate to stratify cardiovascular risk without any further extensive screening of HMOD. This may be considered as a first-line indicator in all hypertensive patients and could be implemented in the baseline workup by GPs. In the case of unavailable ECG, NT-proBNP alone already provides very important prognostic information. We proposed approach is a step-by-step one allowing for a general screening and a tailored use of TTE. TTE should still be considered when plasma NT-proBNP is superior to 125 pg/ml in patients suspected of heart failure and in those with overt heart disease, murmur, and ECG repolarization disorders to add several important informations (left ventricular geometry, systolic and diastolic function, valvular heart disease).

ACKNOWLEDGEMENTS

We thank Philip Robinson (Direction de la Recherche Clinique et de l'Innovation, Hospices Civils de Lyon) for thorough editing of the article.

The study was supported by a grant from the French Federation of Cardiology 'Bourse HTA'.

Conflicts of interest

There are no conflicts of interest.

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