

Left Ventricular Hypertrophy in the Spanish Hypertensive Population. The ERIC-HTA Study

José V. Lozano,^a Josep Redón,^b Luis Cea-Calvo,^c Cristina Fernández-Pérez,^d Jorge Navarro,^e Álvaro Bonet,^e and Jorge González-Esteban,^c on behalf of the ERIC-HTA 2003 research team

^aCentro de Salud Serrería 2, Valencia, Spain.

^bUnidad de Hipertensión Arterial, RECAVA, Hospital Clínico Universitario, Universidad de Valencia, Valencia, Spain.

^cDepartamento de Investigación Clínica, Merck Sharp & Dohme of Spain, Madrid, Spain.

^dUnidad de Apoyo a la Investigación, Hospital Clínico Universitario San Carlos, Universidad Complutense de Madrid, Madrid, Spain.

^eCentro de Salud Salvador Pau, Valencia, Spain.

Introduction and objectives. Left ventricular hypertrophy (LVH) is the earliest manifestation of cardiac damage in hypertension. Its appearance is associated with a poor cardiovascular prognosis. The objectives of this study were to determine the prevalence of electrocardiographic LVH and to assess the epidemiological characteristics of hypertensive patients receiving primary care.

Patients and method. A cross-sectional multicenter study of hypertensive patients aged 55 years or more was carried out in a primary care setting. Blood pressure was measured using the standard method. Cardiovascular history was determined from medical records and LVH was assessed electrocardiographically using Cornell's criteria.

Results. In total, 15 798 patients (mean age 68.0 years, 55.3% women, and 30.4% with diabetes mellitus) were evaluated. Of these, 3207 (20.3%) had electrocardiographic signs of LVH. The prevalence was higher in males, diabetics, smokers, and patients with high blood pressure or renal or cardiovascular disease. Compared to patients without LVH, those with the condition were older, were more often male, and were more likely to have diabetes or renal or cardiovascular disease. Multivariate analysis showed that LVH was independently associated with advanced age, male gender, diabetes, smoking, poor blood pressure control, and the presence of cardiovascular or renal disease. Blood pressure control was poorer in patients with LVH than in those without it.

Conclusions. The prevalence of electrocardiographic LVH is high, with affected patients being more likely to have diabetes or renal or cardiovascular disease. Moreover, blood pressure control is poor in these patients, and

more aggressive pharmacological management is needed.

Key words: Hypertension. Left ventricular hypertrophy. Cardiovascular risk. Blood pressure control.

Hipertrofia ventricular izquierda en la población hipertensa española. Estudio ERIC-HTA

Introducción y objetivos. El objetivo del presente estudio es evaluar la prevalencia de hipertrofia del ventrículo izquierdo (HVI) en el electrocardiograma y el perfil epidemiológico en pacientes hipertensos atendidos en atención primaria.

Pacientes y método. Estudio transversal, multicéntrico, realizado en 15.798 pacientes hipertensos ≥ 55 años de centros de atención primaria. Se midió la presión arterial y se recogieron los antecedentes cardiovasculares de la historia clínica de los pacientes. La HVI se evaluó según los criterios de Cornell.

Resultados. Se evaluó a 15.798 pacientes (edad media, 68,0 años; 55,3% mujeres; 30,4% diabéticos). El 20,3% presentó HVI en el electrocardiograma. La prevalencia fue mayor en varones, diabéticos, fumadores, pacientes con presión arterial no controlada y pacientes con enfermedad renal o con cualquier antecedente de enfermedad cardiovascular. Respecto a los pacientes sin HVI, los pacientes con HVI eran de edad más avanzada, había un mayor porcentaje de varones, y más prevalencia de diabetes mellitus (el 40,5 frente al 27,8%), enfermedad renal (el 34,2 frente al 26,9%) y enfermedad cardiovascular (el 52,1 frente al 20,2%). En el análisis multivariante, la HVI se asoció, de forma independiente, con una edad más avanzada, el sexo masculino, la diabetes, el tabaquismo, la ausencia de control de la presión arterial, y la presencia de enfermedad cardiovascular y renal. El porcentaje de pacientes que cumplían objetivos de control de presión arterial fue menor entre los pacientes con HVI respecto a aquellos sin HVI.

Conclusiones. La prevalencia de HVI en el electrocardiograma es elevada y se asocia con una mayor preva-

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Correspondence: Dr. J. Redón.
Unidad de Hipertensión. Hospital Clínico Universitario
Avda. Blasco Ibáñez, 17. 46010 Valencia. España.
E-mail: josep.redon@uv.es

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ABBREVIATIONS

AHT: arterial hypertension.
 ECG: electrocardiogram.
 LVH: left ventricular hypertrophy.
 BP: blood pressure.
 SBP: systolic blood pressure.
 DBP: diastolic blood pressure.

lencia de diabetes, y enfermedad renal y cardiovascular, además de un control de la presión arterial deficiente.

Palabras clave: Hipertensión arterial. Hipertrofia ventricular izquierda. Riesgo cardiovascular. Control de presión arterial.

INTRODUCTION

Left ventricular hypertrophy (LVH) detected via electrocardiogram (ECG) or echocardiogram is the earliest manifestation of cardiac damage in patients with arterial hypertension (AHT). Electrocardiographic LVH is also an independent risk factor for cardiovascular complications, especially cerebrovascular ones, in the hypertensive population.^{1,2} In addition, patient prognosis is determined by how electrocardiographic LVH evolves and its regression leads to a reduction in cardiovascular complications.^{2,3} As recently demonstrated, electrocardiographic LVH regression predicts regression in the echocardiogram,⁴ and thus ECG appears to be a good follow-up method for this group of patients.

Clinical practice guidelines agree that the aim of treatment in hypertensive patients should be not only to control blood pressure (BP), but protect the target organs affected by hypertension and reduce associated morbidity and mortality.^{5,6} The latest European guideline also emphasizes that the global assessment of cardiovascular risk in the hypertensive patient includes the identification of lesions caused by AHT in the target organs.⁶ Due to its wide availability, the ECG is of particular interest in evaluating and treating the hypertensive patient.

The ERIC-AHT study was designed to estimate stroke risk in the Spanish hypertensive population treated in health centers.⁷ One of the parameters assessed to estimate stroke risk is electrocardiographic LVH.⁸ The aim of the present study is to assess the prevalence of electrocardiographic LVH and the demographic and clinical characteristics of patients in this population.

PATIENTS AND METHOD

The ERIC-AHT is a cross-sectional multicenter epidemiological study of 16 703 patients carried out in primary care centers throughout Spain by approximately

1600 physicians.⁷ The study was approved by an independent clinical research ethics committee and informed consent was given by the participating patients. The data collection period was from June to October 2003.

The study included all hypertensive patients ≥ 55 years of age, whether treated with antihypertensive drugs or not, and undiagnosed or untreated patients who began antihypertensive treatment on the day data were collected. Demographic and anthropometric data were collected as well as those concerning cardiovascular risk factors and a history of cardiovascular disease. Biochemical data were obtained from the patient's medical record and a blood test done 6 months prior to data collection. The study was provided with the OMRON® M5 semiautomatic blood pressure monitor which was used to obtain systolic blood pressure (SBP) and diastolic blood pressure (DBP). The cuff was matched to the perimeter of the arm. After the patient rested for 5 min, 3 BP measurements were done each separated by 2 min. The mean of the last 2 measurements was calculated and taken as the patient's BP. Blood pressure control was considered to have been achieved if this was $<140/90$ mm Hg in non-diabetic patients or $<130/80$ mm Hg in those with diabetes.

The presence of LVH was assessed via ECG in all the patients and evaluated by each investigator. Electrocardiographic LVH was diagnosed according to Cornell criteria: R wave in lead aVL+S wave in lead V3 >28 mm in males and >20 mm in females.⁹ Atrial fibrillation was also assessed via ECG. Serum creatinine levels were evaluated 6 months prior to data collection, and renal function was estimated via the glomerular filtration rate (GFR) calculated with a simplified version of Levey's formula.¹⁰

Statistical Analysis

The sample size was calculated according to the main aim of the study; to estimate stroke risk in the hypertensive population ≥ 55 years old with a 50% stroke risk (risk level assumed in a large sample) based on the 10-year risk of stroke (range, 1%-80%) described in the Framingham study. The sample size was calculated at 14 000 patients. This was done at a 95% confidence interval (CI) with a maximum sampling error of 0.83%.

Qualitative variables are presented with their frequency distribution. Quantitative variables are presented as mean \pm standard deviation (SD) and range. The relationship between qualitative variables was assessed with the χ^2 test or Fisher exact test. Each quantitative independent variable was analyzed with the Mann Whitney U test or median test.

In all cases the distribution of the variable was compared to theoretical models and the assumption of homogeneity of variance was tested. The null hypothesis was rejected in all tests with a type I or alpha error

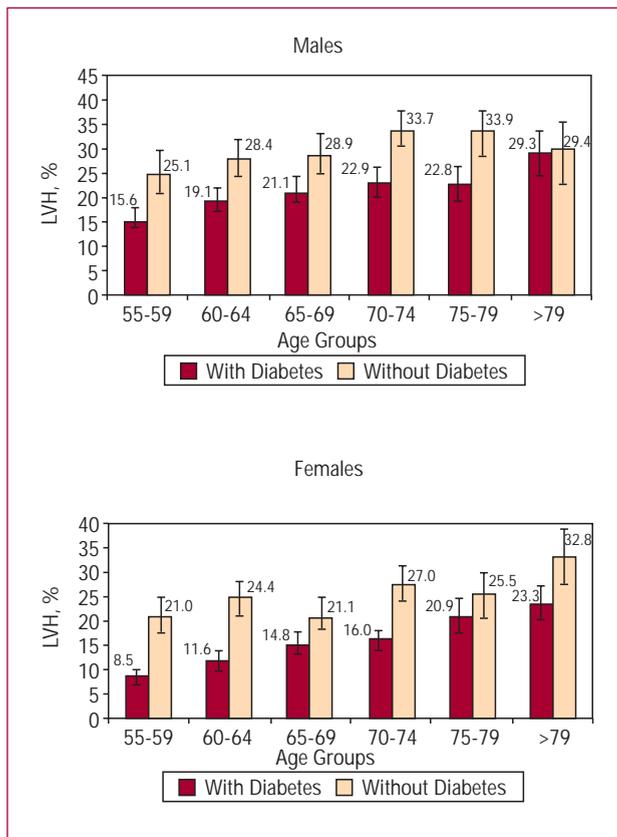


Figure 1. Prevalence of left ventricular hypertrophy in hypertensive patients in the ERIC-AHT study, stratified by age, sex, and presence or not of diabetes mellitus in males (A) and females (B). LVH indicates left ventricular hypertrophy.

<0.05. The SAS version 8.02 software package was used.

RESULTS

Descriptive Data of the Total Sample

Data on 16 129 patients were collected which was valid for 15 798 patients for the ECG analysis (97.9% of the sample, 55.3% females and 44.7% males; mean age, 68.0±8.1 years; range, 55-99). Of these, 30.4% had diabetes and 17.4% were smokers.

Prevalence of Electrocardiographic Left Ventricle Hypertrophy

Electrocardiographic LVH was found in 3,207 patients (prevalence, 20.3%; 95% CI, 19.7-20.9). Figure 1 shows the prevalence of LVH stratified by age, sex, and presence or otherwise of diabetes mellitus. Prevalence was higher in older patients, in males (23.4%) versus females (17.8%), and in diabetic patients (27.1%) versus non-diabetic ones (17.3%) ($P<.001$ for all comparisons). Prevalence did not vary significantly regarding Body Mass Index. The

prevalence of LVH was also significantly higher in patients with BP above control levels versus patients with controlled BP (24.4 vs 17.2%; $P<.001$).

Descriptive Data of Patients With Left Ventricular Hypertrophy

Table 1 presents the descriptive data of hypertensive patients with electrocardiographic LVH compared to those without hypertrophy. The LVH patients were older than those without LVH (mean age, 69.5±8.1 vs 67.6±8.0 years; $P<.001$) and there was a greater percentage of males (51.6% vs 43.0% in patients without LVH; $P<.001$). Of the LVH patients, 40.5% had diabetes mellitus versus 27.8% of subjects those without LVH ($P<.001$). Left ventricular hypertrophy patients had slightly higher serum creatinine levels and slightly lower GFR. Kidney failure was more prevalent among the LVH patients (defined by a GFR<60 mL/min/1.73 m²) than in those without LVH (34.2% vs 26.9%; $P<.001$). There were no differences in the prevalence of excess weight or obesity.

History of Cardiovascular Disease

Table 2 presents the prevalence of a history of cardiovascular disease in patients with and without LVH. The prevalence of any cardiovascular disease was greater in LVH patients (52.1 vs 20.2% in patients without LVH; $P<.001$). Of the LVH patients, 12.2% had a history of myocardial infarction, 21.2% angina, 26.4% heart failure, 17.7% atrial fibrillation, 7.7% stroke, and 12.2% intermittent claudication. In all cases, there was a significantly higher prevalence of a history of cardiovascular disease in LVH patients vs those without LVH ($P<.001$ for all the comparisons).

Blood Pressure Control

In LVH patients, mean SBP was 149.1±17.5 mm Hg and mean DBP 85.0±10.9 mm Hg. In patients without LVH, the mean pressures were 145.9±16.9 and 83.7±10.5 mm Hg, respectively. The differences in SBP (3.3 mm Hg; 95% CI, 2.6-3.9) and DBP (1.3; 95% CI, 0.9-1.7) were statistically significant ($P<.001$). There was a lower percentage of LVH patients with controlled BP (Table 1). Among non-diabetic patients with LVH, 25.1% had BP<140/90 mm Hg, whereas only 5.6% of diabetic patients had BP<130/80 mm Hg. Among patients without LVH, 31.0% of non-diabetic patients and 6.0% of diabetic patients, respectively, had controlled BP ($P<.001$ in non-diabetic patients, $P=.60$ in diabetic ones). Figure 2 presents the percentage of patients with well-controlled BP stratified by sex, presence or not of diabetes mellitus and LVH. Systolic blood pressure was controlled adequately in LVH patients (26.1% in non-diabetic patients vs 7.8% in

TABLE 1. Characteristics of Hypertensive Patients With Left Ventricular Hypertrophy Treated in Primary Care Centers. ERIC-AHT Study*

	Patients Without LVH	Patients With LVH
Age, mean±SD, years	67.6±8.0	69.5±8.1
Sex, %		
Females	57.0	48.4
Males	43.0	51.6
BMI, mean±SD	28.6±4.3	28.8±4.4
BMI Classification, %		
<25	17.6	16.0
25-29.9	51.2	52.1
≥30	31.2	31.9
Smokers, %	16.7	20.2
Diabetes mellitus, %	27.8	40.5
SBP, mean ± SD, mm Hg	145.9±16.9	149.1±17.5
DBP, mean±SD, mm Hg	83.7±10.5	85.0±10.9
Controlled blood pressure, † %	21.8	15.4
Serum creatinine, mean ±SD, mg/dL	1.0±0.4	1.1±0.5
GFR, mean±SD, mL/min/1.73 m ²	74.2±42.9	72.3±52.3
GFR Classification, mL/min/1.73 m ² , %		
<60	26.9	34.2
≥60	73.1	65.8

*SD indicates standard deviation; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

†<140/90 mm Hg, and in diabetic patients <130/80 mm Hg.

P<.001 for all comparisons, except for BMI (P=.028), BMI classification (P=.111), and GFR (P=.088).

TABLE 2. Prevalence of the Different Manifestations of Cardiovascular Disease in Hypertensive Patients With or Without Left Ventricular Hypertrophy Treated in Primary Care Centers. ERIC-AHT Study*

	Patients Without LVH	Patients With LVH	P
Cardiovascular disease (any), %	20.2	52.1	<.001
Chest angina, %	7.4	21.2	<.001
Myocardial infarction, %	4.4	12.2	<.001
Intermittent claudication, %	4.8	12.2	<.001
Heart failure, %	4.5	26.4	<.001
Atrial fibrillation, %	5.4	17.7	<.001
Previous stroke, %	4.0	7.7	<.001
Kidney failure (GFR<60 mL/min/1.73 m ²), %	26.9	34.2	<.001

*GFR indicates glomerular filtration rate; LVH, left ventricular hypertrophy.

diabetic ones) than DBP (62.7% in non-diabetic patients vs 22.1% in diabetic ones). Of the LVH patients, 99.3% were on antihypertensive medication at the time of assessment, of which 46.0% received monotherapy and 54.0% combined treatment. The mean

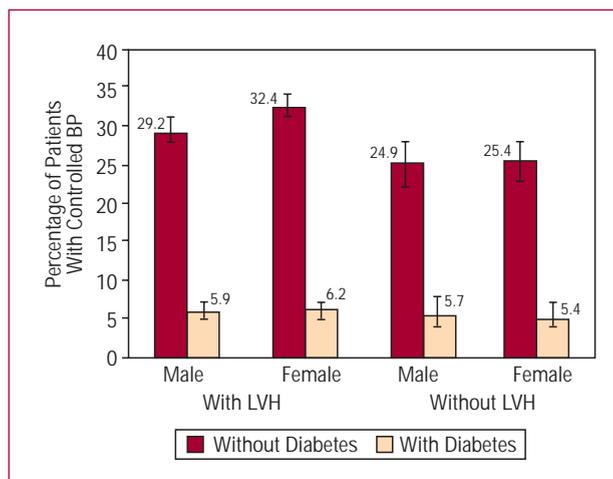


Figure 2. Percentage of patients who achieve blood pressure control goals in the ERIC-AHT study, stratified by sex, diabetes mellitus, and the presence or not of electrographic left ventricular hypertrophy. LVH indicates left ventricular hypertrophy; BP, blood pressure.

number of drugs per patient under treatment was greater in LVH patients vs patients without LVH (mean, 1.7±0.8 vs 1.5±0.7; P<.001).

In addition, for patients with a history of heart failure or with changes in renal function, a BP<130/80 mm Hg was also considered a control target. Thus, in LVH patients with diabetes and/or heart failure and/or changes in renal function, 6.6% had BP<130/80 mm Hg, whereas among LVH patients without such a background 26.2% had BP<140/90 mm Hg. Among patients without LVH, 7.5% and 31.4% reached control targets (P<.001 for both comparisons).

Multivariate Analysis

The logistic regression model used included age, sex, smoking, diabetes, BP control, changes in renal function (GFR<60 mL/min/m²), cardiovascular disease and atrial fibrillation (Table 3). Left ventricular hypertension was independently associated with all the variables, especially with cardiovascular disease or atrial fibrillation. After adjusting for the rest of remaining variables, LVH was also independently associated with changes in renal function and poorly controlled BP.

DISCUSSION

This analysis of the ERIC-AHT study describes the prevalence of electrocardiographic LVH as an expression of early cardiac disease due to AHT, as well as the epidemiological pattern of these patients. Primary care physicians collected data from a sample of non-selected consecutive patients who formed a representative sample of the hypertensive population

TABLE 3. Factors Related to Left Ventricular Hypertrophy. Multivariate Analysis. ERIC-AHT Study*

	OR (95% CI)	P
Sex (male vs female)	1.29 (1.16-1.43)	<.001
Age (1-year increment)	1.01 (1.01-1.02)	<.001
Diabetes mellitus	1.33 (1.20-1.47)	<.001
Smoking	1.26 (1.11-1.43)	<.001
Atrial fibrillation	2.47 (2.13-2.85)	<.001
Vascular disease	3.55 (3.22-3.91)	<.001
Uncontrolled blood pressure	1.37 (1.21-1.54)	<.001
Kidney disease (GFR<60 ml/min/1.73 m ²)	1.28 (1.15-1.43)	<.001

*GFR indicates glomerular filtration rate; CI, confidence interval; OR, odds ratio.

more than 55 years old treated in Spanish health centers.

Electrocardiographic LVH was found in 20.3% of the hypertensive patients. Prevalence was higher in patients at greater cardiovascular risk: males, older patients, diabetic patients and patients with uncontrolled BP. Similarly, and compared to patients without LVH, LVH patients were characterized by advanced age, a greater percentage of males and diabetic patients, poor BP control and a greater prevalence of cardiovascular and renal disease.

The electrocardiogram is the recommended screening method to evaluate the presence of LVH in hypertensive patients⁶, although its sensitivity to detect LVH is low. The use of Cornell criteria can increase sensitivity without losing specificity.² Although no internal validation versus echocardiogram was done in our study as a reference test, Cornell criteria have been evaluated and their value verified in multiple studies. When these criteria were applied, electrocardiographic LVH was reported in 20.3% of patients. In a recently published study, Pascual et al¹¹ described a similar prevalence with the same electrocardiographic criteria in normoalbuminuric patients with mild AHT, although in this study the patients had been referred to a hypertension unit and were younger. Nevertheless, two other primary care studies report dissimilar figures regarding the prevalence of LVH. A similar figure (17.5%) was reported by Barrios et al¹² in the DIORISC study. This study included more than 9000 patients and assessed comorbidity and target organ damage. The most prevalent target organ damage in this population was LVH. However, the PRESCAP study reported a much smaller prevalence of electrocardiographic LVH (7.2%).¹³ Standardizing the definition of LVH by using Cornell criteria (or even better, the Cornell voltage duration product criteria), or by using combined criteria to define the presence of LVH (mainly Cornell and Sokolow-Lyon criteria), can increase the sensitivity of ECG to detect LVH¹⁴ and thus lead to better detection of patients at greater cardiovascular risk. This is

particularly relevant due to the difficulties involved in carrying out systematic echocardiography in such a prevalent disease. Although the prevalence of echocardiographic LVH is much higher than that obtained by ECG,¹⁵⁻¹⁷ the wide availability of ECG promotes its use in any area of the health system.

In our study, patients with electrocardiographic LVH had a higher prevalence of cardiovascular risk factors as well as renal disease (defined as GFR<60 mL/min/1.73 m²) and established cardiovascular disease. Half of the hypertensive patients with electrocardiographic LVH in our series had a cardiovascular complication in contrast to a fifth of the patients without LVH. The presence of LVH in the hypertensive patient is associated with greater cardiovascular morbidity and mortality,^{1,2} and is an independent risk factor for stroke. In a follow-up study of 2363 initially untreated hypertensive patients without cardiovascular disease at the beginning of the follow-up, Verdecchia et al¹⁸ reported that stroke rate was almost double in LVH patients, detected by both ECG and echocardiogram compared to patients without LVH.

The detection of electrocardiographic LVH in the outpatient clinic is essential to assess patient risk and evaluate the effect of antihypertensive treatment on their evolution, since presence or absence of LVH with antihypertensive treatment has prognostic implications in these patients. Whereas electrocardiographic LVH regression is associated with a lower incidence of cardiovascular complications, morbidity and mortality is greater in patients in whom LVH does not regress or progresses.^{2,3,19,20} Two recent analyses of the LIFE study (Losartan Intervention For Endpoint Reduction), carried out in 9193 hypertensive patients with electrocardiographic LVH, showed that LVH regression using electrocardiographic criteria and greater left ventricular mass reduction in the echocardiogram are associated with a lower incidence of cardiovascular disease and lower mortality at follow-up.^{3,21} This information is of special interest regarding the choice of treatment in these patients. The metaanalysis carried out by Klingbeil et al²² reported that different drug classes have different effects on LVH regression: treatment with calcium antagonists, angiotensin enzyme-converting inhibitors or angiotensin II receptor antagonists (ARA-II) yields greater LVH regression than treatment with diuretics or beta-blockers. The LIFE study reported that treatment based on the ARA-II losartan made LVH regress with more efficacy than treatment based on the beta-blocker atenolol. Over time, there was a reduction in cardiovascular morbidity and mortality and the incidence of stroke in patients treated with losartan compared to those treated with atenolol.²³

An aspect of special interest in our study is the higher prevalence of LVH specifically in patients with greater cardiovascular risk (males, older patients, diabetic patients, and patients with poorly controlled BP). Blood pressure control in LVH patients was also worse than in

patients without LVH, with a between-groups difference of 3.3/1.3 mm Hg. The recent ALLHAT and VALUE studies show that even small differences in BP (even lower than those detected among the patients with or without LVH in our study) can have a serious impact on the appearance of cardiovascular complications.^{24,25} This means that, if our population of hypertensive LVH patients is at high risk of cardiovascular events, then this risk is increased due to their higher BP levels.

However, BP control in LVH patients is complex and generally requires the use of high doses of combined drugs. By the end of the LIFE study, 88.5% of the patients were being treated with 2 or more drugs and even so, strict BP control was only achieved in 47.5% of patients.²³ In contrast, in our study, only 54% of LVH patients were treated with combined drugs and less than 25% had controlled BP. Thus, the data show that achieving therapeutic aims is difficult, especially in diabetic and LVH patients; the data also draw to attention the fact that AHT treatment should be pursued more aggressively.

The main limitation of our study is its cross-sectional nature, which places limits on calculating the prevalence of each disease. This can lead to underestimating associations between different variables, especially when some of them (as in the case of stroke) are associated with high mortality in the population presenting them. However, the broad sample of patients included in the study accurately reproduces the findings of day-to-day primary care.

In conclusion, ECG continues to be a very valuable method for detecting LVH and is an essential parameter in the measurement of cardiovascular risk in the hypertensive patient. The prevalence of electrocardiographic LVH when applying Cornell criteria is high and, due to the characteristics of these patients and the poorly controlled BP, ECG identifies a group of patients at high cardiovascular and cerebrovascular risk, as well as those with impaired renal function. Blood pressure control in these patients is difficult and requires the use of combined drugs in high doses. The use of effective drugs for LVH regression which improve cardiovascular prognosis is indicated in this group of special risk patients.

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