

Cardiovascular Morbidity and Mortality and Left Ventricular Geometric Patterns in Hypertensive Patients Treated in Primary Care

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Introduction and objectives. Numerous hospital studies have shown that different left ventricular (LV) geometric patterns have different effects on cardiovascular risk. The aims of this study were to estimate the risk of major adverse cardiovascular events (MACEs) in hypertensive patients seen in primary care and to identify any association with LV geometric pattern.

Methods. In total, 265 hypertensive subjects attending primary care were randomly selected and followed up for 12 years. Those with cardiovascular disease, secondary hypertension, complete bundle branch block or electrocardiographic signs of ischemic heart disease were excluded. The LV geometric pattern was characterized as either concentric hypertrophy, eccentric hypertrophy, concentric remodeling or normal. A MACE was the occurrence of ischemic heart disease, heart failure, stroke, peripheral vascular disease, arrhythmia or cardiovascular death. Data were analyzed using the life-table method and Cox regression modeling.

Results. Although 14% of patients were lost to follow-up, their baseline characteristics were similar to those of patients who completed the study. The cumulative survival rate was 56.3% (95% confidence interval [CI], 49.8-62.8). The incidence of MACEs was 4.67 (95% CI, 3.79-5.55) per 100 subject-years. Moreover, the incidence was similar in the four LV geometric pattern groups ($P=0.889$). Only age (hazard ratio [HR] = 1.03; 95% CI, 1-1.05) and the presence of diabetes at study entry (HR=1.67; 95% CI, 1.03-2.69) were associated with an increased risk of a MACE.

Conclusions. In the study population, only age and diabetes at study entry were associated with the occurrence of a MACE. There was no evidence for an association between MACEs and the LV geometric pattern.

Key words: Hypertension. Left ventricular hypertrophy. Ventricular remodeling. Cardiovascular disease. Primary care. Survival analysis.

Morbimortalidad cardiovascular y patrones geométricos del ventrículo izquierdo en pacientes hipertensos atendidos en atención primaria

Introducción y objetivos. Numerosos estudios hospitalarios muestran el diferente impacto de los patrones geométricos ventriculares izquierdos (VI) en el riesgo cardiovascular. El objetivo fue determinar el riesgo de eventos cardiovasculares (ECV) entre los hipertensos atendidos en atención primaria y analizar su relación con el patrón geométrico VI.

Métodos. Se seleccionó aleatoriamente a 265 hipertensos entre todos los atendidos que fueron seguidos durante 12 años. Se excluyó a los que presentaban enfermedad cardiovascular, hipertensión arterial secundaria, bloqueo completo de rama o signos de cardiopatía isquémica electrocardiográficos. Se los clasificó según el patrón geométrico VI en hipertrofia concéntrica o excéntrica, remodelado concéntrico y normal. Se consideró ECV la aparición de cardiopatía isquémica, insuficiencia cardiaca, accidente cerebrovascular, vasculopatía periférica, arritmias o muerte por ECV. Se analizaron los datos mediante el método actuarial y modelos de regresión de Cox.

Resultados. Se perdió un 14% de los pacientes durante el seguimiento, cuyas características basales fueron similares a las de los que lo completaron. La supervivencia acumulada fue del 56,3% (intervalo de confianza [IC] del 95%, 49,8-62,8). La tasa de incidencia de ECV fue 4,67 (IC del 95%, 3,79-5,55)/100 hipertensos/año. La incidencia de ECV fue similar en los cuatro grupos de patrón geométrico VI ($p = 0,889$). Únicamente la edad (años)

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(*hazard ratio* [HR] = 1,03; IC del 95%, 1-1,05) y la diabetes (HR = 1,67; IC del 95%, 1,03-2,69) al inicio del estudio se asociaron con un mayor riesgo de ECV.

Conclusiones. En la población de estudio sólo la edad y la diabetes al inicio del estudio se asociaron con la aparición de ECV. No se evidenció asociación entre el tipo de patrón geométrico VI y los ECV.

Palabras clave: Hipertensión. Hipertrofia ventricular izquierda. Remodelación ventricular. Enfermedad cardiovascular. Atención primaria de salud. Análisis de supervivencia.

ABBREVIATIONS

BP: blood pressure
 LV: left ventricular
 LVMI: left ventricular mass index
 MACE: major adverse cardiovascular events
 PHC: primary health care
 RPT: relative parietal thickness

INTRODUCTION

Hypertension is one of the most important health problems in developed countries due to its high prevalence and because it is a known risk factor for the development of cardiovascular disease.

Left ventricular (LV) hypertrophy, which is defined as an abnormal increase in LV mass, is one of the organic processes resulting from hypertension. Echocardiography, due to its accuracy, is currently the diagnostic test of choice, although its use is not generalized due to its high cost and lack of accessibility. Therefore, electrocardiography remains the basic complementary test for evaluating cardiac damage in the majority of hypertensive patients attended in primary health care (PHC). Diagnosis of LV hypertrophy is made according to electrocardiographic voltage criteria.

Various studies have demonstrated the role of LV hypertrophy, whether diagnosed by electrocardiography or echocardiography, as an independent cardiovascular disease risk factor associated with increased morbidity and mortality.¹⁻⁷ Different scientific organizations and societies⁸⁻¹⁰ recommend screening for LV hypertrophy in hypertensive patients, as it may modify subsequent therapeutic decisions. Various studies have shown that different LV geometric patterns (identified by echocardiography as concentric hypertrophy, eccentric hypertrophy, or concentric remodeling in the absence of LV hypertrophy) have a different

impact on the risk of cardiovascular disease; with patients with concentric hypertrophy having a higher risk.¹¹⁻¹⁸

Until recently, the few studies determining the prevalence of LV hypertrophy in hypertensive patients had been performed mainly in hospital settings. Given that hypertension is usually detected and controlled in PHC, this implies that PHC patients could be more representative of the general hypertensive population. Moreover, we are not aware of any long-term study that has assessed the prognostic value of LV hypertrophy and the different LV geometric patterns in the general hypertensive population.

In 1993 we began a prospective study⁵ to establish the prevalence of LV hypertrophy, as measured by echocardiography and electrocardiography, in a general hypertensive population free of cardiovascular disease and attended in a PHC center. These patients were then followed-up for several years.^{19,20}

The objective of the study was to determine the risk of major adverse cardiac events (MACE) in a cohort of hypertensive subjects and to analyse their relationship with LV geometric patterns, specially concentric hypertrophy associated with greater cardiovascular risk.

METHODS

The study sample comprised 265 hypertensive subjects randomly selected from patients attended in a PHC center in Barcelona, Spain.^{5,19,20} Follow-up of the cohort lasted 12 years, from April 1993 to April 2005. We included hypertensive subjects aged 18 years or more diagnosed with mild-to-moderate essential hypertension according to World Health Organization criteria.²¹ An initial examination included the measurement of weight, height, and blood pressure (BP), complete physical examination, smoking, general blood chemistry, electrocardiography and echocardiography, and a thorough history of cardiovascular disease. Exclusion criteria were evidence of cardiovascular disease, electrocardiographic abnormalities that were difficult to evaluate, and patients in whom echocardiography could not be performed.

Echocardiography was performed using the TOSHIBA Sonolayer SAL-38D echograph (Toshiba Medical System, An Delft, the Netherlands) with 3.5 and 2.5 MHz transducers. All tests were video-recorded and registered on thermal paper in M mode. Pulse Doppler was used to evaluate LV filling; the sample volume was located 1 mm above the mitral valve level. The tests were performed with the patients in the left lateral decubitus position and standard projections were

used (longitudinal parasternal, 2 and 4 chamber apical, and subcostal). Echocardiography was performed according to the indications of the American Echocardiographic Society and the Penn criteria, with a relative parietal thickness (RPT) <0.44 being used to define normality.^{22,23}

Echocardiograms were recorded by a single cardiologist between February and June 1993. LV geometric patterns were determined in each patient by calculating the left ventricular mass index (LVMI), obtained by dividing the mass of the left ventricle, in grams, by the body surface area, in square meters (g/m^2), and the RPT. LV hypertrophy was defined according to the most-widely used criteria at the time of the study design (Devereux et al²⁴), that is, a LVMI $>134 \text{ g}/\text{m}^2$ in men and $>110 \text{ g}/\text{m}^2$ in women. Hypertensive patients who met both inclusion and exclusion criteria were classified into 4 groups according to LV geometric pattern: concentric hypertrophy (in the case of elevated LVMI and RPT), eccentric hypertrophy (elevated LVMI, normal RPT), concentric remodeling (normal LVMI, elevated RPT), and normal (normal LVMI and RPT).

MACE were defined as the occurrence of the following episodes during the follow-up: heart failure, ischemic heart disease (angina or acute myocardial infarction), stroke (established or transient), peripheral vascular disease (clinical signs of intermittent claudication or demonstrated by echo-Doppler), cardiac arrhythmias (atrial fibrillation, supraventricular paroxysmal tachycardia, and atrial flutter), cardiovascular death, and sudden death. Sudden death was defined as that occurring within 1 hour of the onset of symptoms without witnesses in persons with no previous diagnosis of coronary heart disease or other presumably fatal disease. MACE were recorded during the scheduled follow-up visits for hypertension in the PHC center. Reports of MACE were corroborated by the patients' physicians and hospital or primary care records. In cases in which the scheduled appointments were not kept for a period of 6 months or more, the cause of interruption of the follow-up was investigated. The attending physician or nurse was consulted in the case of a change of address, hospital admission, or admission to an institution. Information on patients lost to follow-up was collected directly from families, friends, or neighbours. If patients could not be located, permission was obtained to inspect local death registries to record the date and cause of death. The MACE and the mortality data were evaluated by an external panel of physicians blinded to the initial type of LV geometric patterns.

The study was approved by the Clinical Investigation Ethical Committee of the IDIAP

Jordi Gol of the Catalan Institute of Health (Comité Ético de Investigación Clínica del IDIAP Jordi Gol del Instituto Catalán de la Salud).

Data analysis was performed using the SPSS package (version 12.0 for Windows). Quantitative data were described as the mean (SD) for data with a normal distribution. In the case of nonnormal distributions, the median and the interquartile range were used. The estimates directly related to the objectives of the study were calculated with the corresponding 95% confidence intervals (CI).

Survival was measured from the date of inclusion to the appearance of MACE, if this occurred. The censored variable was the appearance, or not, of MACE from inclusion in the study (1993) to the end of follow-up (2005). If more than one MACE occurred in the same patient, only the initial event was included in the statistical analysis. Survival curves and the mean relative rates of incidence (hazard ratios) were estimated using the life-table method and curves were compared using the Wilcoxon-Gehan test. The prognostic effects of LV geometric patterns and the adjusted factors were evaluated using Cox proportional risk regression models ("stepwise" method).^{25,26} The initial model was adjusted for the following covariates: age (years), gender (male/female), time since diagnosis of hypertension (months), systolic BP, diastolic BP measured in the last 2 visits, obesity at study entry (body mass index [BMI] $>30 \text{ kg}/\text{m}^2$), diabetes mellitus (DM), dyslipidemia, and tobacco consumption. The assumption of proportional hazards over time was verified for covariables included in the final model.

Other comparisons between groups were made using the χ^2 test, and the Student's *t* test, or analysis of variance, or non-parametric tests when appropriate. The level of statistical significance was established at $P \leq .05$.

RESULTS

The overall prevalence of LV hypertrophy in the study sample was 63.8% (95% CI, 57.7-69.6). The most common type of LV geometric pattern was eccentric hypertrophy (107 cases, 40.4%), followed by normal (68, 25.7%), concentric hypertrophy (62, 23.4%), and concentric remodeling (28, 10.6%). Table 1 summarizes the main patient characteristics at study entry according to LV geometric pattern.

In general, patients with LV hypertrophy, whether eccentric or concentric, were older on average and a greater proportion were women than those without. The mean BMI was lower in patients with eccentric hypertrophy. The distribution of the other variables at study entry was similar between the 4 groups of hypertensive subjects.

TABLE 1. Characteristics of the Cohort of Hypertensive Subjects (n=265) at Study Entry According to Left Ventricular (LV) Geometric Pattern

Characteristic	LV Geometric Patterns				P
	Eccentric Hypertrophy	Concentric Hypertrophy	Concentric Remodeling	Normal	
	n=107	n=62	n=28	n=688	
Age, mean (SD), y	65.9 (9.2)	66.9 (9.1)	61.6 (8.7)	61.6 (10.8)	.003
Females, n (%)	74 (69.2)	47 (75.8)	10 (35.7)	42 (61.8)	.002
Time from hypertension diagnosis, median (IQR), mo	54 (24-120)	60 (24-162)	48 (29-114)	60 (20-120)	.873
Blood pressure (BP) in the last 2 visits, mean (SD), mm Hg					
Systolic BP	161.5 (19.6)	161.1 (15.0)	155.7 (12.6)	154.8 (18.3)	.090
Diastolic BP	89.3 (11.0)	90.8 (9.6)	90.0 (8.2)	88.8 (10.3)	.618
Body mass index, mean (SD), kg/m ²	28.6 (4.3)	30.5 (4.7)	29.3 (3.9)	29.0 (4.4)	.028
Obese, n (%)	33 (30.8)	32 (51.6)	11 (39.3)	28 (41.2)	.064
Diabetes, n (%)	24 (22.4)	9 (14.5)	5 (17.9)	11 (16.2)	.572
Dyslipidemia, n (%)	46 (43.0)	28 (45.2)	8 (28.6)	28 (41.2)	.499
Smoking habit, n (%)	13 (12.1)	10 (16.1)	5 (17.9)	8 (11.8)	.763
Additional cardiovascular risk factors ^a n (%)	76 (71.0)	49 (79.0)	21 (75.0)	48 (70.6)	.656

IQR indicates interquartile range.

^aPatients with hypertension that were obese, diabetic, dyslipidemic, or smokers.

Follow-up was completed by 228/265 patients (86%); 14% were lost to follow-up. There were no differences in baseline characteristics between those who completed follow-up and those who did not.

The median duration of follow-up was 10.2 years (range, 0-12 years). A total of 101 (44.3%) patients suffered at least one MACE during the follow-up. Cumulative survival (hypertensive subjects free of MACE at the end of the study) was 56.3% (95% CI, 49.8-62.8). The mean relative incidence rate of MACE in the study group during the follow-up was 4.67 (95% CI, 3.79-5.55) per 100 hypertensive subjects per year. There was a trend to an increase in MACE up to the eighth year of follow-up and a subsequent decrease (Figure 1). Heart failure, ischemic heart disease, stroke, and peripheral vascular disease were the MACE with the highest rates of incidence during follow-up (Figure 2).

The characteristics of patients at study entry and according to MACE during the follow-up are shown in Table 2. Both the proportion of patients with diabetes and mean age were higher among patients who suffered at least one MACE during the follow-up period. The bivariate analysis showed no significant association between LV geometric patterns and the incidence of MACE. Likewise, there were no significant differences ($P=.889$) according to cumulative survival or the crude rates of incidence of MACE (Figure 3). Similarly, the type of LV geometric pattern, adjusted for the effect of the characteristics of the hypertensive

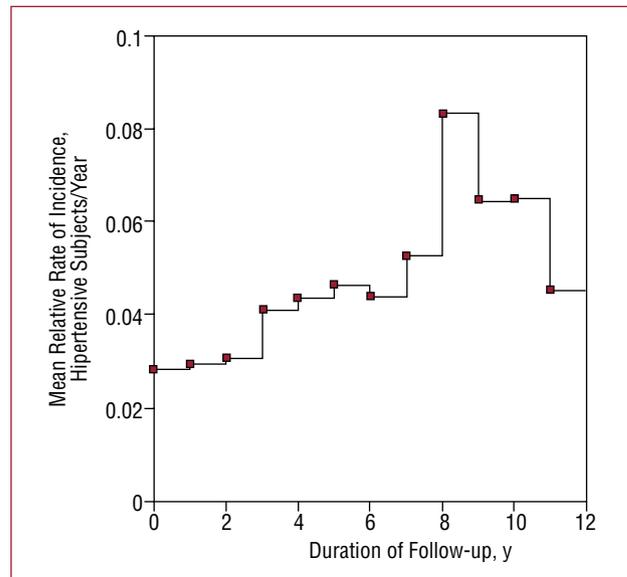


Figure 1. Mean relative rate (unadjusted) of incidence of hypertensive subjects who suffered at least 1 cardiovascular event during the follow-up period.

subjects at study entry (age, gender, time since diagnosis of hypertension, mean systolic BP in the last 2 clinical visits, DM, and dyslipidemia) showed no statistically significant relationship with MACE-free survival in the final equation. Conversely, age and the presence of diabetes were independent predictive factors of MACE (Table 3).

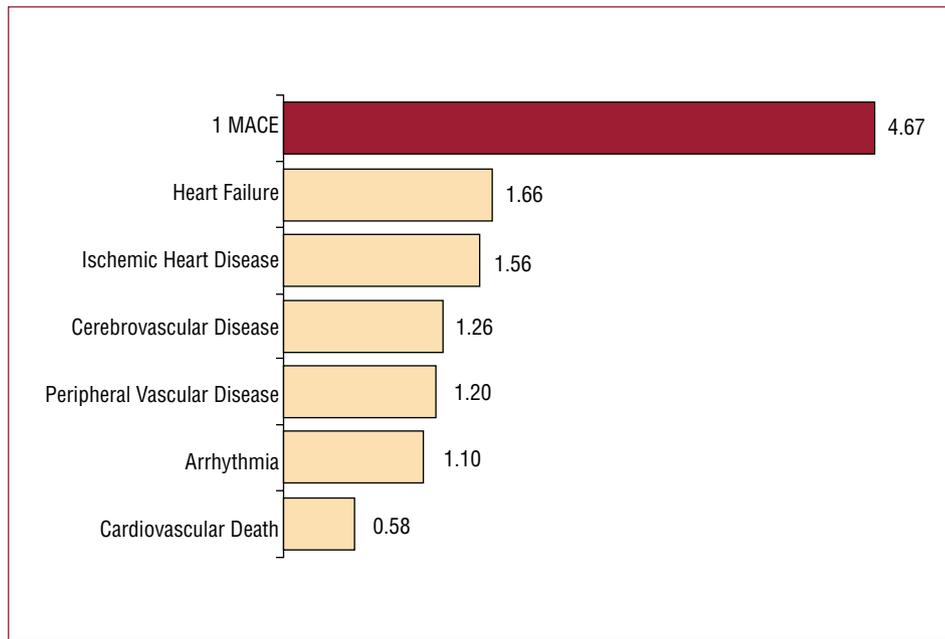


Figure 2. Mean relative incidence rate (unadjusted) per 100 hypertensive subject per year of major adverse cardiovascular events (MACE) observed during follow-up.

TABLE 2. Characteristics of Patients Completing the Study (n=228) at Study Entry According to Whether or Not a Major Adverse Cardiovascular Event (MACE) Occurred During Follow-up

Variables	Total (n=228)	MACE	
		No (n=127)	Yes (n=101)
Age, mean (SD), y	64.0 (10.0)	62.7 (10.9)	65.8 (8.5) ^a
Females, %	65.4	67.7	62.4
Time from hypertension diagnosis, mo	84.5 (91.0)	80.2 (92.7)	89.9 (89.1)
Mean systolic blood pressure (BP) in last 2 visits, mm Hg	158.4 (17.9)	159.4 (18.5)	157.3 (17.3)
Mean diastolic BP in last 2 visits, mm Hg	89.6 (9.9)	90.9 (8.9)	87.8 (10.8)
Body mass index, kg/m ²	29.1 (4.4)	29.0 (4.2)	29.3 (4.7)
Obesity, %	38.6	34.6	43.6
Diabetes, %	17.5	12.6	23.8 ^a
Dyslipidemia, %	41.7	46.5	35.6
Total cholesterol, mmol/L	5.96 (1.16)	5.86 (1.16)	6.08 (1.16)
HDL-C, mmol/L	1.25 (0.34)	1.27 (0.34)	1.24 (0.34)
LDL-C, mmol/L	4.11 (1.08)	4.10 (1.11)	4.12 (1.05)
Creatinine, μmol/L	97 (15.9)	98 (15.9)	96 (16.8)
Smokers, %	13.2	12.6	13.9
Alcohol abuse, %	15.4	18.1	11.9
Additional cardiovascular risk factors, %	72.4	72.4	72.3
None	27.6	27.6	27.7
1	39.9	42.5	36.6
≥2	32.5	29.9	35.6
LV hypertrophy, %	62.3	59.8	65.3
LV geometric patterns, %			
Eccentric hypertrophy	39.9	38.6	41.6
Concentric hypertrophy	22.4	21.3	23.8
Concentric remodeling	11.0	10.2	11.9
Normal	26.8	29.9	22.8
LV mass index, g/m ²	131.2 (33.2)	129.1 (29.5)	133.8 (37.4)
Pharmacologic treatment, %	72.4	71.7	73.3

BP indicates blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LV, left ventricular.

^aP<.03 versus the patients who remained free of MACE.

The quantitative variables are presented as means (SD).

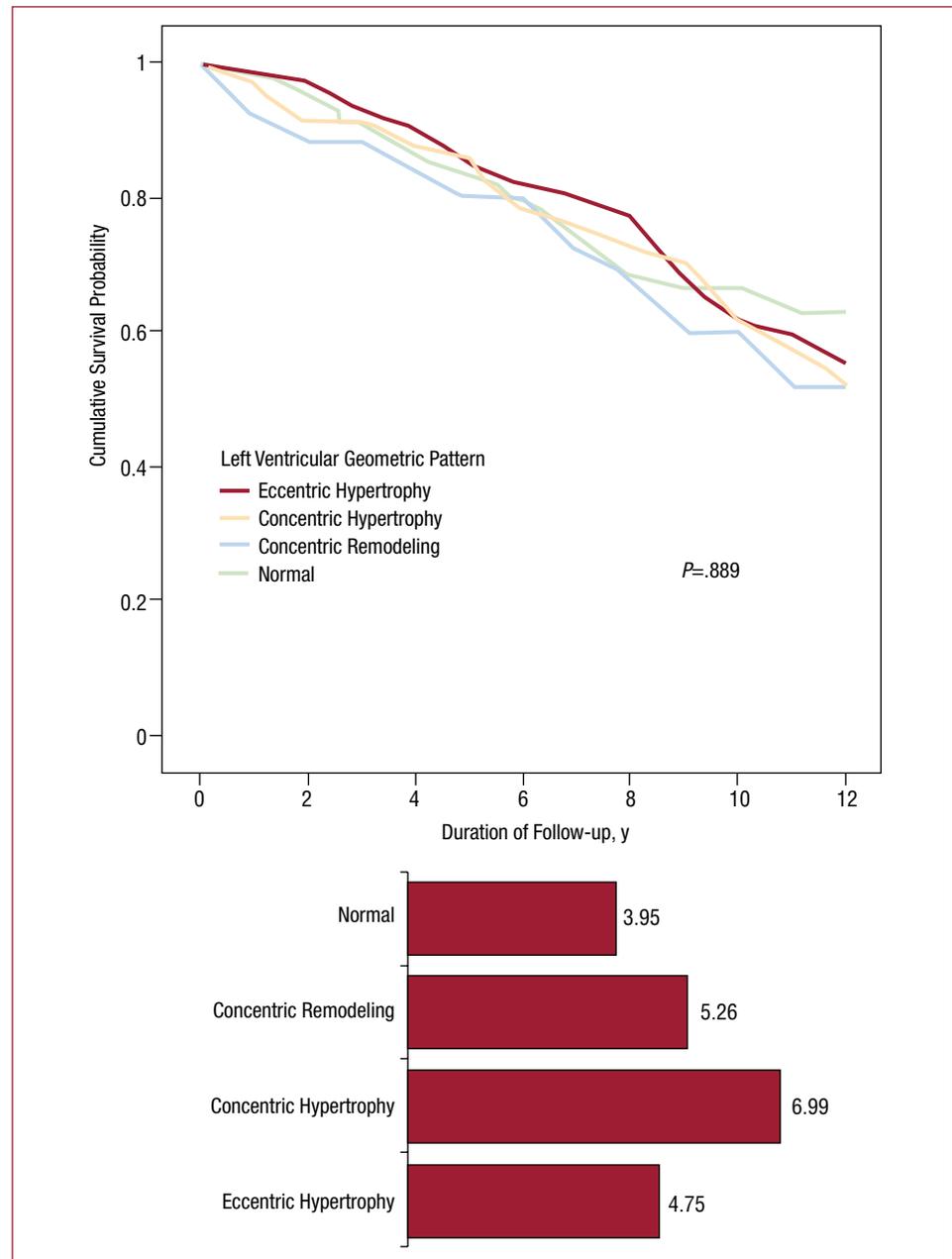


Figure 3. Cumulative survival probability of hypertensive subjects free of major adverse cardiovascular events (MACE) and mean relative incidence rate (unadjusted) per 100 hypertensive persons per year of MACE according to left ventricular (LV) geometric pattern in the cohort of hypertensive subjects.

DISCUSSION

We found no significant evidence of an association between LV geometric patterns and the incidence of cardiovascular disease. Patients without LV hypertrophy did not have higher cumulative survival. Although the role of LV hypertrophy as an independent cardiovascular risk factor for cardiovascular morbidity and mortality in both men and women appears to be well established,¹⁻⁴ we found that other cardiovascular risk factors may play a more important role in PHC patients, in whom age and diabetes at study entry better explained the incidence of MACE.

Reports on the prevalence of LV geometric patterns and their association with MACE vary widely. Possible explanations include the length of follow-up and the inclusion of cohorts in a hospital setting, which could easily behave differently to the general population. In addition, there may be geographical differences in the epidemiology of cardiovascular disease between northern European or American populations and southern European ones, as in the present study.^{1-4,7,11-20,24,27-30}

Koren et al¹¹ in 1991 using a similar design and sample size, with a cohort of 253 patients followed for approximately 10 years, found a strong association between LV hypertrophy and the risk of

TABLE 3. Final Cox Regression Model to Estimate the Adjusted Effect of Left Ventricular (LV) Geometric Patterns on Major Acute Cardiovascular Events in the Cohort of Hypertensive Subjects

Variables	Comparison	Hazard Ratio (95% CI)	P
Eccentric hypertrophy	Normal	1.11 (0.66-1.90)	.689
Concentric hypertrophy	Normal	1.15 (0.63-2.13)	.645
Concentric remodeling	Normal	1.39 (0.68-2.83)	.362
Age	1 y	1.03 (1.00-1.05)	.029
Sex	Male versus female	1.48 (0.96-2.28)	.079
Time since diagnosis of hypertension	≥5 years versus <5 years	1.38 (0.92-2.09)	.123
Mean systolic blood pressure in the last 2 visits	1 mm Hg	0.99 (0.98-1.00)	.085
Diabetes mellitus	Yes versus no	1.67 (1.03-2.69)	.036
Dyslipidemia	Yes versus no	0.70 (0.46-1.07)	.096

CI indicates confidence interval; HR, hazard ratio.

MACE, with a cumulative incidence of MACE in patients with and without LV hypertrophy of 26% and 12%, respectively. In our study, the cumulative incidence observed was 43.7% at 12 years, with no differences according to presence or absence of LV hypertrophy. However there are differences between the 2 studies with respect to the type and selection of sample studied, the diagnostic criteria, and the type of MACE recorded. Patients included in the study by Koren et al were selected from patients attending cardiology units and were Americans, both of which imply a greater cardiovascular risk compared with our Mediterranean population.

Several authors have found an association between MACE and LV geometric pattern, mainly with concentric hypertrophy¹¹⁻¹⁸ and this is reflected in the latest guidelines.⁸⁻¹⁰ However, the findings are not consistent since studies by the same investigators have reached contradictory conclusions. For example, Watchell et al⁷ and Devereux et al⁴ found no differences between LV geometric patterns in relation to MACE. Conversely, more recent studies such as that of Verdecchia et al^{27,28} and Gerds et al²⁹ in which concentric remodeling was grouped together with concentric and eccentric hypertrophy, found a higher risk of cardiovascular disease.

A possible limitation of the present study is the number of patients lost to follow-up due to its long duration as compared to other shorter studies, which could result in selection bias that would adversely affect the internal validity. However, the high frequency of visits and accessibility helped to ensure an optimum follow-up. In addition, patients unable to attend successive appointments to control their hypertension were contacted by telephone or visited at home.

The use of a specific questionnaire for data collection, together with the use of computerized clinical records and death registries has been also

very useful. In our PHC setting the computerized clinical history has been used since 1998. The computerized protocols of health-care provision greatly facilitated the registration and retrieval of variables analyzed in the present study.

The final percentage of patients lost to follow-up was 14%, similar to the 10% observed in the study by Koren et al.¹¹ There were no significant differences in the characteristics of those lost to follow-up and those who finished the study. Koren et al found that age and race (younger and African-American subjects) were associated with a greater probability of drop-out from the study. In addition, they did not include patients with diabetes or other types of MACE such as stroke without permanent sequelae, arrhythmias, and peripheral artery disease. These differences together with the use of more restrictive criteria for the diagnosis of LV hypertrophy in women in our study (110 g/m²) may have contributed to our finding of no evidence of association between the different LV geometric patterns and the incidence of MACE.

Another limitation was the reduced sample size, especially in the concentric remodeling group. This could have increased the probability of a type II error. Although a comparison of cases with and without LV hypertrophy would have increased the power of the study, the true objective was to determine the difference in the incidence of MACE between the different LV geometric patterns.

Another problem was lack of longitudinal follow-up of some of the measurements, that is, some changes in baseline measurements were not analyzed during long-term follow-up. We were not able to assess antihypertensive or concomitant treatment such as statins or antiplatelet therapy during follow-up, a situation that could have affected outcomes. Neither did we evaluate changes in microalbuminuria, which was not recorded at

study entry (1993). However, our methodology aimed to ensure that the sample was representative, unlike that of other studies such as those of Koren et al¹¹ and Verdecchia et al,²⁷ who used consecutive selection. The homogeneity of the different groups compared and correct measurement of the variables reduced the possibility of selection and information biases and increased the internal validity of the study.

The external validity of the study is limited to patients attending our PHC center. However, in our environment, public health-care coverage is high (72% in 2006). Extrapolation of the study sample to the general population seems acceptable since it is at this level of health-care provision that the majority of the hypertensive population receive clinical attention.³¹ These aspects, together with the acceptable percentage of loss to follow-up, make this study of interest to PHC professionals.

CONCLUSIONS

Approximately half the study population suffered at least one MACE, occasionally fatal, during follow-up (12 years). We found no association between LV geometric patterns and the incidence of cardiovascular disease in this study, conducted in a representative sample of the general hypertensive population treated in a PHC center.

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