ORIGINAL RESEARCH

Impact of Chamber Dilatation on the Prognostic Value of Left Ventricular Geometry in Hypertension

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***Background*—**The different geometric patterns of the left ventricle may or may not coexist with chamber dilatation. The prognostic impact of such a combination is unclear.

***Methods and Results*—**We studied a cohort of 2635 initially untreated patients with hypertension, mean age 50 years. At entry, 24-hour ambulatory blood pressure progressively increased across the patterns of normal geometry, concentric left ventricular (LV) remodeling, eccentric nondilated LV hypertrophy (LVH), eccentric dilated LVH, concentric nondilated LVH, and concentric dilated LVH. During a mean follow-up of 9.7 years, 360 patients developed a first major cardiovascular event at a rate (×100 patient-years) of 1.41. The event rate was 0.93 in the group with normal LV geometry, 1.10 in the group with LV concentric remodeling, 1.40 in the group with nondilated eccentric LVH, 2.10 in the group with eccentric dilated LVH, 2.34 in the group with nondilated concentric LVH, and 4.67 in the group with dilated concentric LVH (log-rank test: $P<0.001$). In a Cox model, after adjustment for several independent covariables (age, sex, diabetes mellitus, current smoking, total cholesterol, estimated glomerular filtration rate, and average 24-hour systolic blood pressure), concentric dilated LVH was associated with a 98% excess risk of cardiovascular events ($P=0.0037$). However, LV geometric pattern lost statistical significance when LV mass was entered into the model.

***Conclusions*—**In initially untreated patients with hypertension, LV dilatation adds an adverse prognostic burden to the patterns of eccentric and concentric LVH. This phenomenon is explained by the greater LV mass associated with LV chamber dilatation. **(*J Am Heart Assoc*. 2017;6:e005948. DOI: 10.1161/JAHA.117.005948.)**

Key Words: ambulatory blood pressure monitoring • echocardiography • geometry • left ventricular hypertrophy • left ventricular mass

The prognostic value of echocardiographic left ventricular (LV) mass[1,2] and its regression with treatment[3–6] are well established. During the past 2 decades, several studies have suggested that the geometric pattern of the left ventricle may improve cardiovascular risk stratification in patients with hypertension.[2,7–10] LV geometry can be described by calculating the relative wall thickness as a function of septum or posterior wall thickness divided by the internal diameter at telediastole.[11] In outcome-based studies, the risk of major cardiovascular disease was higher in patients with concentric remodeling than in those with normal LV geometry,[2,9] and also greater in patients with concentric LV hypertrophy (LVH) than in those with eccentric LVH.[10] However, since LV mass (LVM) is usually greater in patients with concentric remodeling than in those with normal geometry,[9] and also greater in patients with concentric LVH than in those with eccentric LVH,[10] the independent prognostic value of LV geometry was weakened or abolished because of the overwhelming prognostic impact of LVM itself.[7,8,10]

More recently, in a study based on magnetic resonance imaging, Khouri and coworkers[12] found a lower LV ejection fraction and higher values of troponin and other surrogate markers of cardiovascular risk in patients with LV chamber dilatation associated with both concentric and eccentric patterns of LVH. Consequently, they suggested reclassifying concentric and eccentric LVH into 2 groups based on the absence or presence of LV dilatation.[12]

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Accompanying Tables S1 and S2 and Figure S1 are available at http://jaha.ahajournals.org/content/6/6/e005948/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What is New?

- Adjusting for several established risk factors (age, sex, diabetes mellitus, current smoking, total cholesterol, estimated glomerular filtration rate, and average 24-hour systolic blood pressure), LV chamber dilatation is associated with adverse prognosis in both the eccentric and concentric patterns of LVH in patients with hypertension, and this phenomenon was explained by the greater LVM associated with chamber dilatation.

What are the Clinical Implications?

- This 4-tiered categorization of LVH is an alternative to LVM to refine cardiovascular risk stratification in patients with hypertension. Patients with LV chamber dilatation and LVH may be candidates for more aggressive strategies to mitigate cardiovascular risk.

In a longitudinal study from Italy, eccentric dilated LVH and concentric dilated and nondilated LVH were associated with a higher risk of major cardiovascular events when compared with normal LV geometry in patients with hypertension.[13] However, the potential confounding effect of several variables including 24-hour ambulatory blood pressure (BP) was not evaluated. In another study from Italy, the prognostic value of eccentric nondilated and eccentric dilated LVH lost significance when LVM was added to the model.[14] However, this study had not enough size to assess the prognostic value of chamber dilatation associated with concentric LVH.[14]

None of the studies that addressed the impact of chamber dilatation on the prognostic value of LV geometry have been specifically conducted in large cohorts of patients with hypertension who were untreated at the time of initial assessment. Additionally, long duration of follow-up and availability of several clinical and experimental confounders measured at baseline were not always present in earlier reports. Accordingly, we examined a large observational study of initially untreated patients with hypertension in whom baseline assessment of echocardiographic parameters, ambulatory BP, and several variables were available.

Methods

The PIUMA (*Progetto Ipertensione Umbria Monitoraggio Ambulatoriale*) study, established in June 1986, is a prospective observational registry of morbidity and mortality in initially untreated patients with hypertension. The registry was approved by the local ethics committee of the Italian National Health Service and all patients provided their informed consent to participate. Details of the study have been published elsewhere.[5,9,15] Entry criteria included an office systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg on at least 3 visits and absence of secondary causes of hypertension, previous cardiovascular disease, or life-threatening conditions. Shift workers were excluded. BP was measured by a physician with a mercury sphygmomanometer with the patient sitting and relaxed for at least 10 minutes. The cuff size was adjusted to the patient's arm circumference. Three measurements were averaged for analysis. Systolic and diastolic BP were identified by Korotkoff phases I and V.

Ambulatory BP

Ambulatory BP was recorded using an oscillometric device (SpaceLabs 520016, 9020217, and 9020718). Frequency of measurements was set to 1 every 15 minutes throughout the 24 hours. Daytime and nighttime ambulatory BP were defined through the use of a diary reporting the times of awakening and retiring. Reproducibility of ambulatory BP readings in our patients was examined in a previous study in which a random sample of untreated patients with hypertension included in the PIUMA registry repeated 24-hour BP monitoring within 3 to 5 days.[16] The between-session coefficient of variability (SD of the mean of the paired differences between 2 sessions divided by the average of all paired means) was 5.9%/6.3% for daytime BP and 6.1%/6.3% for nighttime BP.[16]

Echocardiography

M-mode echocardiographic study of the left ventricle was performed under 2-dimensional guide, according to recommendations of the American Society of Echocardiography.[17] Only frames with optimal visualization of interfaces and showing simultaneous visualization of septum, LV internal diameter, and posterior wall were used for reading. Details about reading procedures and reproducibility in our laboratory have been previously reported.[5,9,18] LVM was calculated by using a necropsy validated formula[19] and corrected by height in meters at the power of 2.7.[20] LVH was defined by an LVM >47.0 g/height[$m^{2.7}$] in women and >50.0 g/height[$m^{2.7}$] in men.[21] Concentric LV geometry was defined by a relative wall thickness >0.43 in both men and women,[13] and LV chamber dilatation by an LV internal diameter at end diastole >3.30 cm/height[m] in women and >3.34 cm/height[m] in men.[13] The calculation of different phenotype is illustrated in Figure S1.

Follow-Up

We tailored treatment on an individual basis by using lifestyle and pharmacological measures. Follow-up of patients was the responsibility of family doctors, in collaboration with our

hospital staff. We planned periodical contacts with family doctors and phone interviews and clinical visits with patients in order to ascertain the vital status and occurrence of events.

Assessment of End Points

We reviewed in conference all hospital records and other source documents of patients who died or experienced a cardiovascular event. Events were adjudicated by the authors of this study. We defined a composite pool of major cardiovascular events as terminating end points. The composite pool included cardiovascular death, nonfatal stroke or myocardial infarction, transient ischemic attack, hospitalization for heart failure, unstable angina, coronary revascularization, arterial occlusive disease, or dialysis. We also performed sensitivity analysis restricted to harder events, with exclusion of transient ischemic attack and unstable angina. Cardiovascular death was defined as a sudden cardiac death or a death caused by acute myocardial infarction, acute stroke, heart failure, or other cardiovascular causes. The international standard criteria used to diagnose outcome events in the PIUMA study have been described elsewhere.[15,22]

Data Analysis

Data analysis was performed using SPSS version 18 (SPSS Inc) and SAS release 9.2 (SAS Institute Inc). We reported parametric data as mean±SD. The distribution of antihypertensive drug treatments across the different phenotypes was tested using the chi-square test. We restricted survival analysis to the first-occurring event in patients who experienced multiple events. Survival curves were estimated by the Kaplan–Meier product-limit method. We tested the effect of prognostic factors on survival using Cox semiparametric regression models. The proportional hazards assumption was tested and verified with Schoenfeld residuals. We derived the hazard ratios after adjustment for the following variables: age, sex (women, men), diabetes mellitus (no, yes), current smoking (no, yes), total cholesterol (mmol/L), estimated glomerular filtration rate based on the Modification of Diet in Renal Disease formula, and average 24-hour systolic BP.[23] We also used the Akaike information criterion[24] and the Bayesian information criterion[25] to compare non-nested models including either the different LV geometric patterns, or LVM, in addition to the other covariables in the model. Akaike information criterion is equal to −2(log-likelihood)+2K, where K is the number of covariables included in the model plus the intercept.[24] The model with the lowest Akaike information criterion is considered the "best" among the candidate models being tested. When assessing the Bayesian information criterion, which identifies more parsimonious models,[25] the preference for the model with the lowest Bayesian information criterion should be strong for differences >10 and strong for differences between 6 and 10.[26]

Two-sided $P \leq 0.05$ were considered statistically significant.

Results

Figure 1 shows the flow diagram of the study. Overall, we enrolled 3792 consecutive patients in the PIUMA study from June 12, 1986, to June 11, 2006. After exclusion of patients with incomplete follow-up information, clinical normotension, or unavailable echocardiographic tracings, 2635 patients entered the study. These patients were followed for an average of 9.7 years. Their main characteristics are shown in Table 1. The mean age was 50 years, and 52% were women. Overall, 43% of patients showed normal LV geometry, 21% showed eccentric LV hypertrophy (31% of whom with LV dilatation), and 22% showed concentric LV hypertrophy (5% of whom with LV dilatation). Office BP and 24-hour ambulatory BP (Figure 2) progressively increased from normal LV geometry to concentric LV remodeling, eccentric LV hypertrophy, and concentric LV hypertrophy. The same pattern was shown by echocardiographic LVM, which was consistently higher in patients with LV dilatation associated with either eccentric or concentric LV hypertrophy (Figure 2).

Table S1 reports the distribution of antihypertensive drug treatments at the last contact before cardiovascular event or censoring. Diuretics or β-blockers alone or combined, inhibitors of the renin-angiotensin system pathway alone or combined, and calcium channel blockers alone or combined were used more frequently in individuals with LVH, regardless of the geometric pattern or chamber dilatation, than in individuals with normal LVM (all $P<0.001$). By contrast, α_1 receptor blockers, alone or combined with different drug classes, did not show any differences between the groups ($P=0.90$).

Outcome Events

Cardiovascular events

During a mean follow-up period of 9.7 years, 360 patients developed a first major cardiovascular event (Figure 1). There were 82 patients with nonfatal myocardial infarction, 78 with nonfatal stroke, 34 with cardiovascular death (sudden cardiac death in 13), 67 with unstable angina with or without coronary revascularization, 33 with transient ischemic attack, 29 with heart failure leading to hospitalization, 27 with peripheral occlusive disease, and 10 who started dialysis. The event rate was 1.41×100 patient-years (95% CI, 1.27–1.56). The event rate was 0.93 in patients with normal LV geometry, 1.10 in patients with LV concentric remodeling, 1.40 in

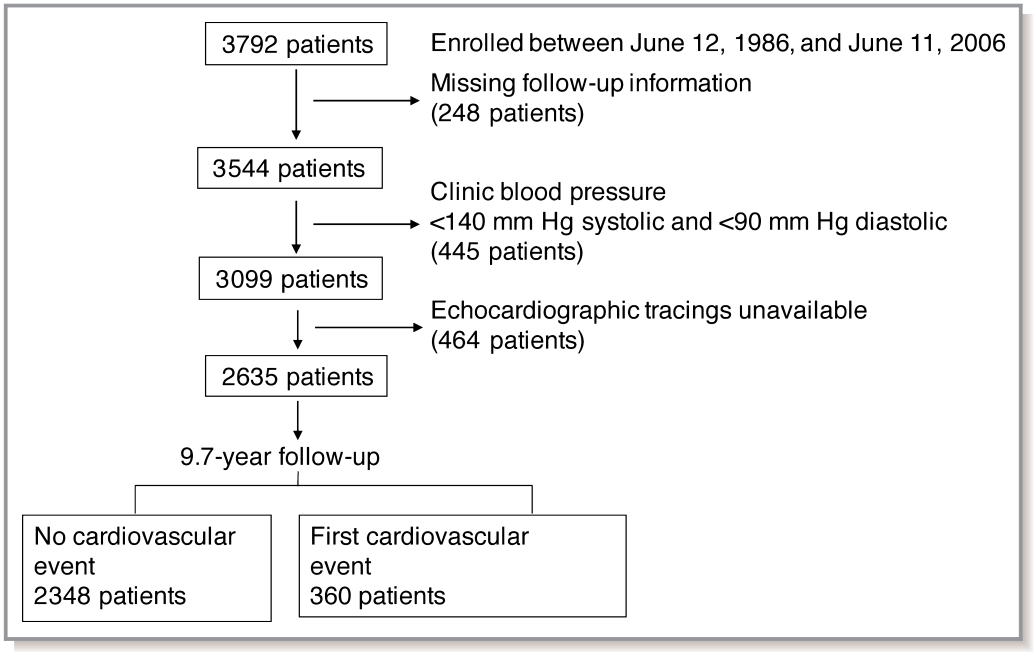

Figure 1. Flow chart of the study.

patients with nondilated eccentric LVH, 2.10 in patients with eccentric dilated LVH, 2.34 in patients with nondilated concentric LVH, and 4.67 in patients with dilated concentric LVH (log-rank test, $P<0.0001$). Survival curves are reported in Figure 3.

In a multivariable analysis (Table 2), after adjustment solely for age and sex, eccentric dilated LVH and both patterns of concentric LVH were associated with a significant excess risk of cardiovascular events. However, after adjustment for age, sex, diabetes mellitus, current smoking, total cholesterol, estimated glomerular filtration rate, and average 24-hour ambulatory systolic BP, eccentric dilated and concentric nondilated LVH lost statistical significance. When LVM was added to the model, concentric dilated LVH totally lost statistical significance ($P=0.806$). The same trend was maintained (Table S2) when transient ischemic attack and unstable angina were not included as end points.

When comparing different multivariable non-nested models, we found lower values of Akaike information criterion (4702 versus 4713) and Bayesian information criterion (4749 versus 4783) in the model that included LVM compared with the model that included the different LV geometric patterns with or without chamber dilatation, in addition to the other covariables.

Discussion

In this large cohort of initially untreated patients with hypertension, LV chamber enlargement increased the risk of major cardiovascular disease in patients with both eccentric and concentric LVH. Notably, the prognostic impact of LV dilatation remained significant when controlling for several significant and well-established risk factors including age, sex, diabetes mellitus, current smoking, total cholesterol, estimated glomerular filtration rate, and 24-hour systolic BP. However, when LVM was included into the model, the excess risk associated with LV geometry, with or without dilatation, was no longer significant for cardiovascular disease. Thus, LV geometry and dilatation did not add prognostic information not captured by LVM.

Previous Studies

The present study strengthens and extends the conclusions of some previous investigations on the prognostic impact of LV enlargement combined with the different patterns of LV geometry in patients with hypertension. The concept of combining LV chamber dilatation with the eccentric and concentric patterns of LVH stemmed from an analysis by Khouri and coworkers of the Dallas Heart Study.[12] In that study, patients with LV chamber dilatation, associated with both concentric and eccentric patterns of LVH determined through magnetic resonance imaging, showed lower values of LV ejection fraction and higher levels of troponin.[12] The authors suggested to subdivide eccentric and concentric LVH into 2 subgroups based on the absence or presence of LV chamber dilatation.[12] In a subsequent analysis of their study, LV dilatation portended a higher risk of cardiovascular death and heart failure regardless of the pattern of eccentric or concentric LVH.[27] However, the number of outcome events

Table 1. Main Features of the Population

Variable	All Patients (N=2635)	Normal LV Geometry (n=1132)	Concentric LV Remodeling (n=373)	Eccentric Nondilated LVH (n=385)	Eccentric Dilated LVH (n=176)	Concentric Nondilated LVH (n=540)	Concentric Dilated LVH (n=29)	*P* Value
Age, y	50 (12)	47 (11)	49 (11)	51 (11)	53 (11)	53 (12)	56 (11)	<0.001
Body mass index, kg/m^2	26.7 (4)	26.7 (3)	25.6 (3)	27.7 (4)	29.1 (4)	28.1 (4)	28.9 (5)	<0.001
Known duration of hypertension, y	3.9 (6)	3.3 (5)	3.4 (5)	3.9 (5)	4.5 (7)	5.0 (7)	7.9 (9)	<0.001
Women, %	51.7	50.4	40.2	43.6	48.3	37.2	51.7	<0.001
Diabetes mellitus, %	6.6	5.3	4.8	3.9	13.1	9.6	20.7	<0.001
Current smokers, %	24.6	20.7	27.7	24.7	26.1	29.8	27.6	0.007
Total cholesterol, mmol/L	5.57 (1.1)	5.58 (1.1)	5.61 (1.1)	5.62 (1.1)	5.55 (1.2)	5.50 (1.1)	5.69 (1.3)	0.608
HDL Cholesterol, mmol/L	1.28 (0.3)	1.32 (0.3)	1.29 (0.3)	1.28 (0.3)	1.22 (0.3)	1.22 (0.3)	1.20 (0.3)	<0.001
LDL cholesterol, mmol/L	3.59 (0.9)	3.58 (0.9)	3.64 (0.9)	3.63 (1.0)	3.61 (1.0)	3.49 (0.9)	3.88 (1.0)	0.180
Glucose, mmol/L	5.49 (1.1)	5.39 (1.0)	5.43 (1.1)	5.52 (1.2)	5.70 (1.2)	5.63 (1.2)	6.19 (2.1)	<0.001
Uric acid, mmol/L	281 (82)	268 (79)	287 (85)	287 (83)	292 (82)	296 (79)	313 (899)	<0.001
Office BP								
Systolic, mm Hg	156 (19)	150 (15)	153 (17)	158 (19)	161 (16)	165 (20)	181 (27)	<0.001
Diastolic, mm Hg	97 (10)	96 (8)	97 (9)	98 (10)	97 (10)	100 (12)	103 (19)	<0.001
Average 24-h ambulatory BP								
Systolic, mm Hg	137 (15)	131 (11)	136 (12)	139 (14)	140 (15)	146 (16)	160 (20)	<0.001
Diastolic, mm Hg	87 (10)	84 (8)	87 (9)	88 (10)	87 (10)	91 (11)	97 (17)	<0.001
Interventricular septum thickness, cm	1.11 (0.23)	0.96 (1.15)	1.12 (0.14)	1.19 (0.17)	1.11 (0.19)	1.34 (0.22)	1.40 (0.19)	<0.001
LV internal diameter, cm	4.96 (0.52)	4.95 80.43)	4.43 (0.36)	5.25 (0.35)	5.78 (0.45)	4.83 (0.40)	5.61 (0.30)	<0.001
Posterior LV wall thickness, cm	1.00 (0.18)	0.87 (0.11)	1.06 (0.09)	1.01 (0.10)	1.00 (0.14)	1.23 (0.15)	1.33 (0.12)	<0.001
Relative LV wall thickness, %	0.41 (0.09)	0.35 80.05)	0.48 (0.05)	0.38 (0.03)	0.35 (0.05)	0.51 (0.07)	0.47 (0.03)	<0.001
LVM, g/height[m$^{2.7}$]	48.6 (14)	38.9 (6)	40.9 (5)	55.6 (6)	65.4 (14)	61.4 (11)	89.7 (12)	<0.001
Cardiovascular events, No.	360	105	37	54	37	116	11	

P values refer to 1-way ANOVA for continuous variables and chi-square test for categorical variables. BP indicates blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; LVH, left ventricular hypertrophy; LVM, left ventricular mass.

was small (n=81) and the multivariable analysis could not assess the impact of several potential confounders including cholesterol, smoking, renal function, and LVM.[27]

In the Campania Salute Network, a large Italian registry of initially treated and untreated patients with hypertension,[13] after adjustment for LVM, age, sex, diabetes mellitus, and body mass index, the prognostic impact of LV chamber dilatation combined with the geometric patterns of the left ventricle was no longer significant.[13]

Our study extends the conclusions of the above studies to a large cohort of initially untreated patients with hypertension who were followed for a longer time (9.7 years). We used a robust statistical model, which controlled for 24-hour systolic BP and other covariables including glomerular filtration rate. In a general population study conducted in initially treated and untreated patients from Northern Italy, Cuspidi and coworkers[14] found a significantly higher risk of cardiovascular and all-cause deaths in patients with dilated and nondilated eccentric LVH as well as in patients with concentric LVH. However, since none of their patients fulfilled the criteria for concentric dilated LVH, the impact of this important geometric pattern could not be assessed.[14] Such a limitation likely reflects the lower office BP at entry in that general population study[14] than in the present study, which was performed in patients with hypertension (132/84 mm Hg versus 160/90 mm Hg).

LV Geometry

In a study conducted by our group in patients with hypertension with normal LVM, the adverse prognostic impact of LV concentric remodeling remained significant even after adjustment for LVM.[9] In a similar analysis conducted in patients with more severe hypertension and echocardiographic evidence of LVH, the prognostic value of eccentric and concentric LVH disappeared after controlling for LVM.[10]

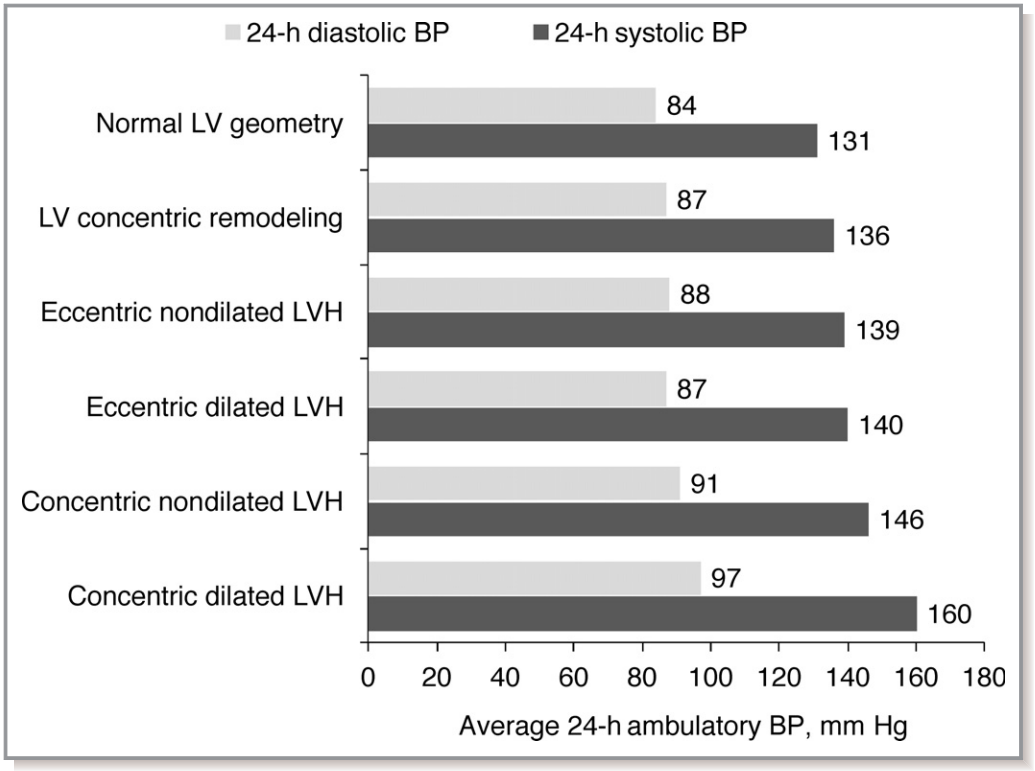

Figure 2. Twenty-four-hour ambulatory systolic and diastolic blood pressure (BP) with the different patterns of left ventricular (LV) geometry associated, or not, with LV dilatation. LVH indicates left ventricular hypertrophy.

Comparable data emerged from the Cardiovascular Health Study.[28] In that study, the risk of incident heart failure was higher in patients with concentric LV remodeling than in those with normal LV geometry in the group with normal LVM, while the impact of LV geometry was no longer significant in the group with LVH.[28] The ascendancy of LVM over geometry for

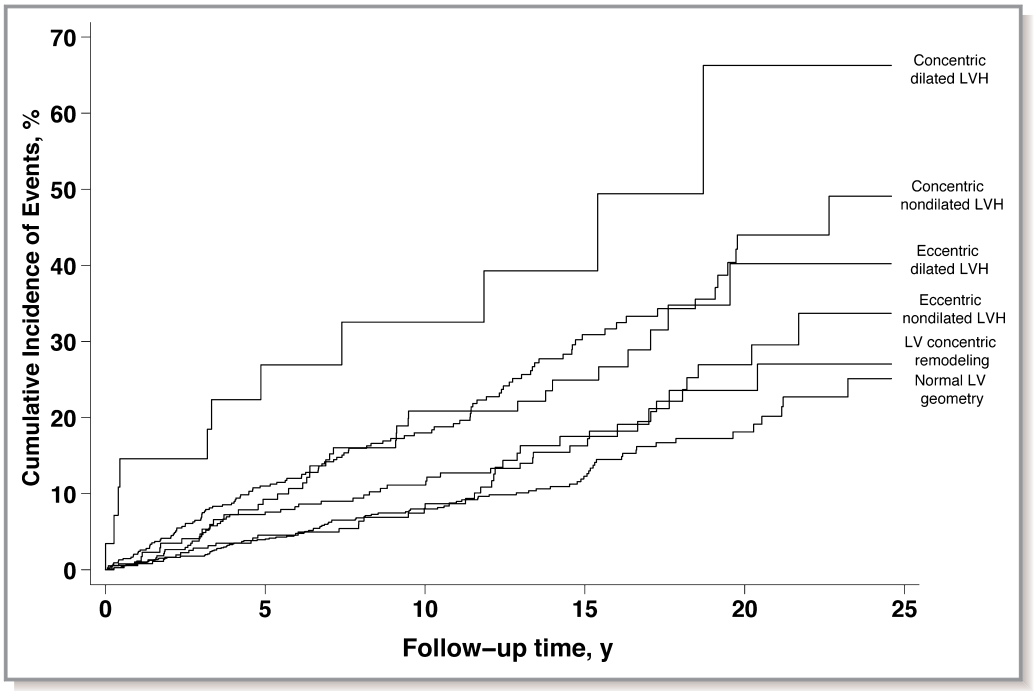

Figure 3. Kaplan–Meier curves of major cardiovascular events in relation to the different patterns of left ventricular (LV) geometry associated, or not, with LV dilatation. LVH indicates left ventricular hypertrophy.

Table 2. Results of Multivariable Analysis for Total Cardiovascular Events

Covariable	Comparison	Hazard Ratio (95% CI)	*P* Value
Model 1			
Normal LV geometry		1	
LV concentric remodeling		1.015 (0.692–1.479)	0.939
Eccentric nondilated LVH		1.190 (0.855–1.654)	0.302
Eccentric dilated LVH		1.673 (1.146–2.441)	0.008
Concentric nondilated LVH		1.798 (1.372–2.356)	<0.001
Concentric dilated LVH		3.823 (2.051–7.125)	<0.001
Age	1 y	1.059 (1.048–1.070)	<0.001
Sex	Male vs female	1.958 (1.568–2.445)	<0.001
Model 2			
Normal LV geometry		1	
LV concentric remodeling		0.922 (0.629–1.350)	0.676
Eccentric nondilated LVH		1.014 (0.720–1.429)	0.935
Eccentric dilated LVH		1.266 (0.847–1.893)	0.250
Concentric nondilated LVH		1.305 (0.973–1.750)	0.076
Concentric dilated LVH		1.984 (1.043–3.772)	0.037
Age	1 y	1.048 (1.037–1.060)	<0.001
Sex	Male vs female	1.808 (1.430–2.285)	<0.001
Diabetes mellitus	Yes vs no	1.737 (1.275–2.367)	<0.001
Current smoking	Yes vs no	1.633 (1.294–2.061)	<0.001
Total cholesterol	1 mmol/L	1.171 (1.062–1.291)	0.001
Estimated GFR	1 mL/min per 1.73 m^2	0.988 (0.980–0.995)	0.001
Average 24-h SBP	1 mm Hg	1.024 (1.016–1.031)	<0.001
Model 3			
Normal LV geometry		1	
LV concentric remodeling		0.922 (0.629–1.350)	0.676
Eccentric nondilated LVH		0.861 (0.590–1.254)	0.345
Eccentric dilated LVH		0.937 (0.568–1.547)	0.800
Concentric nondilated LVH		1.034 (0.713–1.499)	0.862
Concentric dilated LVH		1.113 (0.474–2.612)	0.806
Age	1 y	1.048 (1.036–1.049)	<0.001
Sex	Male vs female	1.744 (1.376–2.211)	<0.001
Diabetes mellitus	Yes vs no	1.735 (1.273–2.364)	<0.001
Current smoking	Yes vs no	1.624 (1.287–2.051)	<0.001
Total cholesterol	1 mmol/L	1.179 (1.069–1.299)	0.001
Estimated GFR	1 mL/min per 1.73 m^2	0.988 (0.981–0.995)	0.001
Average 24-h SBP	1 mm Hg	1.021 (1.013–1.029)	<0.001
LVM	1 g/height[$m^{2.7}$]	1.012 (1.000–1.023)	0.041

The covariables listed above have been included in each of the 3 models. GFR indicates glomerular filtration rate; LV, left ventricular; LVH, left ventricular hypertrophy; LVM, left ventricular mass; SBP, systolic blood pressure.

cardiovascular risk stratification has been confirmed by Krumholz and coworkers in an analysis of the Framingham Heart Study.[8] In that study, the odds ratio for incident cardiovascular disease in patients with concentric LVH compared with those with normal geometry was 1.3 (95% CI, 0.8–2.1) in men and 1.2 (95% CI, 0.6–2.3) in women after

controlling for LVM and other cardiovascular risk factors.[8] In contrast, LVM and relative wall thickness were independent predictors of all-cause death, cardiovascular death, and hospitalization for heart failure in patients with acute myocardial infarction included in the VALIANT (Valsartan in Acute Myocardial Infarction) echocardiographic study.[29] Partially different findings have been reported by Huang and coworkers in a patient population with coronary artery disease undergoing coronary angiography.[30] In that study, LV dilatation conferred a higher risk of subsequent cardiovascular events and all-cause death regardless of the geometric pattern of LVH.[30] However, it was unclear whether the adverse prognostic impact of LV dilatation was explained by greater LVM.

Study Strengths and Limitations

Our results are strengthened by involving a large cohort of patients with hypertension who were untreated at entry, thus avoiding the potential interference of previous antihypertensive treatment. In addition, adjustment for 24-hour ambulatory BP and other well established risk factors added precision to our estimates. Our results are based on an open registry and can thus be subjected to selection bias. However, although results of echocardiographic studies were disclosed to the general practitioners who followed these patients in the setting of our health system, it is unlikely that results of LV geometry and chamber enlargement affected the choice of drug treatment. Notably, since our study was conducted in a white population, results should not be extended to other ethnic groups or to treated patients at the time of initial echocardiographic assessment. In addition, the relatively small size of the group with dilated concentric LVH limited our findings. However, this group showed a high rate of major cardiovascular events (4.67×100 patient-years). Finally, the potential impact of longitudinal variations of LV geometric patterns and LV chamber enlargement could not be investigated.

Conclusions

In initially untreated patients with essential hypertension, LV chamber dilatation identified a high-risk subphenotype of eccentric and concentric LVH. Based on this and other[13,14,27,30] studies conducted in diverse populations and settings, such 4-tiered categorization of LVH is emerging as a valuable operational approach, a potential alternative to LVM, to refine cardiovascular risk stratification in patients with hypertension. Although further studies are needed in this area, these data raise the possibility that patients with LV chamber dilatation associated with LVH are candidates for a more aggressive strategy to control their cardiovascular risk. Notably, from a statistical standpoint, such classification is not superior to LVM taken as a continuous variable, most likely because LVM is roughly sensitive to chamber dilatation by including LV internal diameter in its computation.[31]

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Antihypertensive drug treatment at the last contact before cardiovascular event or censoring in the different phenotypes.

Variable	Normal LV geometry	Concentric LV remodeling	Eccentric non-dilated LVH	Eccentric dilated LVH	Concentric non-dilated LVH	Concentric dilated LVH	p value
Diuretics or beta-blockers*	511 (47%)	167 (46%)	206 (54%)	97 (56%)	296 (55%)	19 (65%)	< 0.001
ACE inhibitors or AT_2 receptor blockers*	523 (48%)	188 (51%)	245 (64%)	98 (56%)	340 (64%)	20 (69%)	< 0.001
Calcium channel blockers*	221 (20%)	72 (20%)	123 (32%)	54 (31%)	188 (35%)	12 (41%)	< 0.001
$Alpha_1$ blockers or other classes*	65 (6%)	28 (8%)	23 (6%)	10 (6%)	35 (6%)	2 (7%)	0.90

Abbreviations: * = Alone or combined; ACE=angiotensin converting enzyme; AT_2=angiotensin 2; LV=left ventricular; LVH = left ventricular hypertrophy.

Table S2. Results of multivariable analysis for hard cardiovascular events.

Covariable	Comparison	Hazard Ratio (95% confidence Interval)	p value
Model 1			
Normal LV geometry		1	
LV concentric remodelling		1.111 (0.737-1.677)	0.614
Eccentric non-dilated LVH		1.157 (0.793-1.687)	0.450
Eccentric dilated LVH		1.939 (1.288-2.919)	0.002
Concentric non-dilated LVH		1.785 (1.314-2.425)	< 0.001
Concentric dilated LVH		4.114 (2.063-8.205)	< 0.001
Age	1 year	1.057 (1.045-1.069)	< 0.001
Sex	Male vs Female	2.499 (1.928-3.273)	< 0.001
Model 2			
Normal LV geometry		1	
LV concentric remodelling		0.971 (0.640-1.473)	0.889
Eccentric non-dilated LVH		1.927 (0.626-1.373)	0.705
Eccentric dilated LVH		1.373 (0.886-2.127)	0.156
Concentric non-dilated LVH		1.186 (0.851-1.654)	0.314
Concentric dilated LVH		1.856 (0.908-3.796)	0.090
Age	1 year	1.044 (1.032-1.057)	< 0.001
Sex	Male vs Female	2.290(1.743-3.009)	< 0.001
Diabetes	Yes vs No	1.655 (1.165-2.352)	0.005
Current smoking	Yes vs No	1.720 (1.331-2.221)	< 0.001
Total cholesterol	1 mmol/l	1.248 (1.120-1.390)	< 0.001
Estimated GFR	1 cc/min	0.985 (0.977-0.994)	0.001
Average 24-hour SBP	1 mmHg	1.028 (1.019-1.036)	< 0.001
Model 3			
Normal LV geometry		1	
LV concentric remodelling		0.972 (0.641-1.475)	0.895
Eccentric non-dilated LVH		0.775 (0.505-1.189)	0.243
Eccentric dilated LVH		0.984 (0.567-1.707)	0.954
Concentric non-dilated LVH		0.917 (0.604-1.393)	0.685
Concentric dilated LVH		0.983 (0.382-2.532)	0.972
Age	1 year	1.044 (1.031-1.057)	< 0.001
Sex	Male vs Female	2.206 (1.675-2.906)	< 0.001
Diabetes	Yes vs No	1.655 (1.165-2.352)	0.005
Current smoking	Yes vs No	1.709 (1.323-2.208)	< 0.001
Total cholesterol	1 mmol/l	1.257 (1.128-1.401)	< 0.001
Estimated GFR	1 cc/min	0.985 (0.977-0.994)	0.001
Average 24-hour SBP	1 mmHg	1.025 (1.016-1.034)	< 0.001
LV mass	1 g/height(m)$^{2.7}$	1.013 (1.000-1.025)	0.042

The covariables listed above have been forced in each of the three models. LVH=left ventricular hypertrophy; GFR=glomerular filtration rate.

Figure S1. Calculation of the different phenotypes of left ventricular hypertrophy based on left ventricular geometry and chamber dilatation.