# Validation of a new 4-group Classification of Left Ventricular Hypertrophy Based on Left Ventricular Geometry in a Population-Based Sample: The Strong Heart Study

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## Abstract

**Objective:** To evaluate the prognostic value of a 4-group left ventricular (LV) hypertrophy (LVH, high LV mass [LVM]) classification based on LV dilatation (high LV end-diastolic volume [EDV] index) and concentricity (LVM/EDV) in a population-based sample.

**Background:** LVH is traditionally classified as concentric or eccentric based on LV relative wall thickness. However, a 4-group LVH classification might predict survival more accurately.

**Methods:** 3,178 American Indian participants with high body mass index (BMI, 30.4 kg/m$^2$), and prevalence of diabetes (48.5%) and who had measurable LVM were followed for a mean of 11.5 years. 618 with LVH (LVM/height$^{2.7}$ ≥50 g/m$^{2.7}$) were divided into 4 groups; "eccentric non-dilated" (normal LVM/EDV [≤1.7g/mL (women) or ≤1.8g/mL (men)] and EDV [<85 ml/m$^2$]), "eccentric dilated" (increased EDV, normal LVM/EDV), "concentric non-dilated" (increased LVM/EDV, normal EDV), "concentric dilated" (increased LVM/EDV and EDV). LVH classes were tested for association with all-cause and cardiovascular mortality in multivariable Cox analyses.

**Results:** At baseline, LVs were categorized as "eccentric non-dilated" in 12%, "eccentric dilated" in 3%, "concentric non-dilated" in 4%, "concentric dilated" in <1% and without LVH in 81%. In Cox analyses adjusting for age, sex, body mass index, kidney function, systolic blood pressure and diabetes compared to participants without LVH, both groups of eccentric and both groups of concentric LVH had increased risk of all-cause and cardiovascular mortality regardless of dilatation and baseline differences. However, there was a clear trend for worse outcome in the dilated compared to the non-dilated subgroups.

**Conclusions:** In a population-based sample of American Indians with high prevalences of obesity and diabetes, participants with dilated eccentric LVH and dilated concentric LVH had increased risk of all-cause and cardiovascular mortality compared to the non-dilated subgroups.

**Key Words:** left ventricular geometry, risk prediction, left ventricular hypertrophy, echocardiography

## Abbreviations

BMI = body mass index

BSA = body surface area

CI = confidence interval

EDV = end-diastolic volume

eGFR = estimated glomerular filtration rate

LV = left ventricle

LVH = left ventricular hypertrophy

LVM = left ventricular mass

MRI = magnetic resonance imaging

RWT = relative wall thickness

SD = standard deviation

SHS = Strong Heart Study

Left ventricular (LV) hypertrophy (LVH), as defined by increased LV mass (LVM), can occur through ventricular dilation, wall thickening or combinations thereof. To discriminate among these patterns of hypertrophy, LVH has been sub-classified based on relative wall thickness (RWT) i.e. wall thicknesses/radius[1]. If the ratio is high, the term "concentric" is used; if not the term "eccentric" is applied. Using magnetic resonance imaging (MRI) measurements this 2-category classification of LVH has been further subdivided into four groups, reclassifying participants with eccentric LVH with normal LV end-diastolic volume (EDV) into a subgroup with better LV function.[2] This new 4-group classification system has not yet been related to clinical outcome in a population-based sample with high prevalence of diabetes and obesity.

We therefore evaluated baseline differences and hemodynamic patterns as well as cardiovascular and all-cause mortality in the new 4-group LVH classification based on LV concentricity (high LVM/EDV) and LV dilatation (high EDV/ body surface area [BSA]) in American Indians with high prevalence of diabetes and obesity.

## Methods

### Study Design

The Strong Heart Study (SHS) is a population-based cohort study of cardiovascular risk factors and prevalent/incident cardiovascular disease in American Indian communities in Arizona, Oklahoma, and South Dakota/North Dakota, as described in detail previously.[3-6] At enrollment in 1989 to 1992, the study cohort included adults aged 45 to 74 years in participating communities. Extensive characterization of participants included standardized measurement of seated brachial blood pressure, body mass index (BMI), fasting glucose, insulin, lipid, and lipoprotein concentrations; and 2-hour glucose tolerance test and glycosylated hemoglobin levels. Arterial hypertension was defined by recommendations of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[3] Diabetes mellitus was diagnosed by World Health Organization criteria[7] or current use of hypoglycemic

therapy. Microalbuminuria was defined as urine albumin/creatinine ≥30 and <300 mg and macroalbuminuria as albumin/creatinine ≥300 mg/g. A total of 3,501 participants in the second SHS examination (between 1993 and 1995) underwent an echocardiographic examination[4] and were considered for the present study. The Indian Health Service Institutional Review Board and institutional review boards of the participating institutions and participating tribes approved the study; informed consent was obtained from all participants.

Participants with prevalent coronary heart disease, stroke, or congestive heart failure at the time of echocardiographic examination were excluded from the present analysis.

Echocardiography

All echocardiograms were evaluated centrally at Weill Cornell Medical Center, New York, NY. To standardize echocardiogram performance, sonographers for each center underwent a specific training course at the reading center. As described previously, echocardiograms were performed with phased array echocardiographs with M-mode, 2D, pulsed- and continuous wave and color-flow Doppler capabilities.[8] Correct orientation of imaging planes was verified by standard procedure.[9] End-diastolic LV dimensions were used to calculate LVM with a necropsy-validated formula.[10] LVM was indexed for body height$^{2.7}$.[11] End-diastolic and end-systolic LV volumes, calculated by z-derived method,[12] were used to calculate the ejection fraction. Wall motion was assessed by a visual, semi-quantitative method in parasternal long and short-axis and apical views. According to Mayo Clinic criteria, the LV was divided into 5 segments at the base and papillary muscle levels (anterior and posterior septum and anterior, lateral, and inferior walls) and into 4 apical segments (septum, anterior, lateral, and inferior walls).[13] Segments were scored as having normal systolic wall thickening (≥30%) or as having mild (wall thickening 20% to 29%), moderate (wall thickening 10% to 19%), or severe (wall thickening ≤10%) hypokinesia, or as being akinetic or dyskinetic.[14] Segmental wall motion abnormalities were considered present for the analyses discussed here if present in 2 contiguous segments in a coronary territory. Hypokinesis was

classified as global when it symmetrically involved all segments or segmental if predominantly localized to specific segments. As previously described,[15] we evaluated LV performance taking end-systolic stress into account, observed midwall shortening was expressed as a percentage of the value predicted from circumferential end-systolic stresses using equations derived from previously studied normal subjects; for convenience, this variable is termed stress corrected midwall shortening. Stress-corrected midwall shortening, an estimate of myocardial contractility, was calculated as percent-predicted midwall shortening by given end-systolic stress.[12]

Defining Left Ventricular Geometry

LVH and increased LVEDV/BSA were defined as ≥98$^{th}$ percentile of an apparently normal population (n=362) from New York:[16] LVM/ height$^{2.7}$: ≥50 g/m$^{2.7}$ and LVEDV/BSA: ≥85 mL/m$^2$ (Figure 1). We used non-gender specific partition for LVH, which we previously have shown to predict prognosis better compared to a gender-specific partition.[17] To indentify wall thickening we calculated an LV concentricity index as proposed by Khouri et al..[2] The concentricity index is calculated as k x (LV myocardial volume/LVEDV), as previously described.[2] Because preliminary analyses showed that the LVM/LVEDV was more highly correlated with RWT than LVM/LVEDV$^{(2/3)}$ in our data (gender adjusted $r^2$=0.67 and 0.35, respectively), we used LVM/LVEDV for concentricity. Gender specific values for LVM/LVEDV (termed concentricity) were defined as ≥98$^{th}$ percentile of an apparently normal population (n=362) from New York:[16] ≥1.7 g/mL in women and ≥1.8 g/mL in men. The LVH patients were then grouped into 4 groups based on whether concentricity and LVEDV/BSA were increased or not using the above threshold values. To parallel the standard 2-group classification, we classified hypertrophy as concentric when concentricity exceeded the above sex-specific thresholds and as eccentric when it was below those values. To test whether the results were dependent on the method of indexing LVM for body size, two sensitivity analyses were performed: 1) RWT was used to define concentricity (>0.45, defined as 98$^{th}$ percentile in a reference population (n=362));[16] and 2) LVM was indexed by BSA to define

LVH (LVM/BSA ≥106 g/m$^2$ (women) and ≥114 g/m$^2$ (men), defined as ≥98$^{th}$ percentile of an the reference population).[16, 18]

Endpoints

Observation for endpoints extended from the date of echocardiography to the end of 2006. Fatal and nonfatal cardiovascular events, including myocardial infarction, stroke, coronary heart disease, and heart failure, were identified from sources in each community and through annual follow-up of participants and verified through death certificates and review of medical records, as described previously.[4, 19] An independent review panel of physicians who were blinded to echocardiographic data adjudicated events as previously described.[19-21] Follow-up for nonfatal events and mortality was 99% and 99.8% complete, respectively. The primary endpoint in this post-hoc study was all-cause mortality and the secondary endpoint was cardiovascular death.

Statistical Analysis

Descriptive data are reported as mean±standard deviation (SD) and frequencies expressed as percentages. Continuous variables without normal distribution were log transformed as appropriate and expressed as median with interquartile range. Differences in categorical variables were evaluated using Chi-square and continuous variables using 1-way ANOVA and non-parametric values were tested with Kruskal–Wallis rank-sum test. To test if the 4-group classification system was prognostically relevant, LVH groups at baseline were analyzed with normal LVM as the reference group in both uni- and multivariable Cox regression. Multivariable Cox models were adjusted for age, gender, BMI, estimated glomerular filtration rate (eGFR), systolic blood pressure and baseline diabetes mellitus. Proportional-hazard assumptions and lack of interactions were tested for each model and confirmed unless otherwise reported. Finally, the event-free survival of patients was evaluated with the Kaplan–Meier method and the log rank test.

SAS statistical software package version 9.2 for PC (SAS Institute Inc, Cary, NC) was used for statistical analyses. Two-tailed $p < 0.05$ was regarded as statistically significant.

## Results

Among the 3,178 eligible participants with needed baseline LV dimensions there were 1,214 all-cause and 403 cardiovascular deaths during follow-up for a mean of 11.5 years.

Using the new 4-group classification system, 376/3,178 (11.8%) had eccentric non-dilated, 96 (3.0%) eccentric dilated, 138 (4.3%) concentric non-dilated, and 8 (0.3%) had concentric dilated LVH and 2,560 (80.7%) had normal LVM (Figure 1). Using the traditional 2-classification system based on concentricity, the first two groups were classified as eccentric LVH (n=472) and the latter two groups as concentric LVH (n=146) (Figure 1).

None of the 3,178 patients had concentric LV remodeling (defined as no LVH but increased concentricity).

Baseline Characteristics and Cardiac Structure and Function between Groups

Participant characteristics in patients grouped by the new criteria are shown in Table 1 and echocardiographic measures of cardiac structure and function are shown in Table 2. Participants in the concentric LVH groups (with or without LV dilation) had higher systolic blood pressure, urine albumin/creatinine ratio, eGFR and concentricity (by definition) than those without concentric LVH.

To determine whether the 4-group classification system identified distinct subgroups of patients, baseline characteristics within the non-dilated vs. dilated subgroups of eccentric and concentric LVH were compared. Among participants with eccentric LVH, those with eccentric dilation had lower BMI, RWT, Doppler stroke volume, cardiac output, midwall shortening, LV ejection fraction; and higher systolic blood pressure, heart rate, urine albumin/creatinine ratio, left atrial diameter dimension in systole, LVM/BSA and mitral valve E/A ratio; and more were men, had diabetes and segmental wall motion abnormalities.

Among participants with concentric LVH, those with dilated LVs had lower BMI, RWT, LV ejection fraction and midwall shortening; and higher systolic blood pressure, heart rate, eGFR, urine albumin/creatinine ratio, high sensitivity C-reactive protein, LA diameter, LVM/BSA, cardiac output, Doppler stroke volume, cardiac output and mitral valve E/A ratio; and more had segmental wall motion abnormalities (Table 1 & 2).

Comparison of Subjects with Eccentric Non-Dilated Hypertrophy to Those without Left Ventricular Hypertrophy

By definition, participants with eccentric non-dilated LVH had increased LVM/ height$^{2.7}$ but did not meet criteria for concentricity or LV dilatation. Compared to participants without LVH the eccentric non-dilated LVH group were older and had higher systolic blood pressure, BMI, urine albumin/creatinine ratio, high-sensitivity C-reactive protein, LA diameter, LVM/BSA, Doppler stroke volume, cardiac output and midwall shortening; but lower RWT, total peripheral resistance index, LV ejection fraction, midwall shortening; and were older and more had segmental wall motion abnormalities (Table 1 & 2).

All-cause Mortality in Respect to the 2 Different Classification Systems of Left Ventricular Hypertrophy

All-cause mortality occurred in 1,214 (38%) participants: 234 (50%) with eccentric, 108 (74%) with concentric and 872 (34%) in participants without LVH. When using the 2-group classification system both eccentric (HR: 1.71 [95%CI: 1.48-1.97]) and concentric LVH (HR: 3.24 [95%CI: 2.66-3.96], both $p<0.001$) were associated with all-cause mortality in univariable and multivariable Cox models (HR: 1.51 [95%CI: 1.24-1.84] and HR: 2.31 [95%CI: 1.76-3.03], both $p<0.001$, respectively, Figure 2a).

When analyzing the subgroups of LVH using the new 4-group classification system, all-cause mortality occurred in 158 (42%) with eccentric non-dilated, 76 (79%) with eccentric dilated, 102 (74%) with concentric non-dilated and 6 (75%) with concentric dilated LVH (Table 3

and Figure 3). In univariate analyses both eccentric non-dilated and dilated were associated with higher risk of all-cause mortality compared to patients without LVH (HR: 1.32 [95%CI: 1.12-1.57], p=0.001 and HR: 4.35 [95%CI: 3.44-5.51], p<0.001, respectively). In multivariable Cox models, both non-dilated and dilated eccentric LVH remained associated with increased all-cause mortality; and the later substantially stronger than the former (HR: 1.38 [95%CI: 1.12-1.71], p=0.003 and HR: 2.51 [95%CI: 1.66-3.80], p<0.001), respectively) (Figure 2b). In the concentric group, both LVH groups were associated with all-cause mortality in univariate (HR: 3.19 [95%CI: 2.60-3.92] and HR: 4.85 [95%CI: 2.17-10.83], respectively, both p<0.001), but in multivariate analyses the dilated LVH did not remain significant because of the small number of cases (non-dilated HR: 2.33 [95%CI: 1.77-3.05], p<0.001 and dilated HR: 1.86 [95%CI: 0.46-7.53], p=0.38, respectively, Figure 2b).

Cardiovascular Mortality in Respect to the 2- and 4-group Classification Systems of Left Ventricular Hypertrophy

During follow-up cardiovascular death occurred in 403 (13%) patients: 97 (21%) in the eccentric, 44 (30%) in the concentric and 262 (10%) in the group without LVH. Using the 2-group classification both eccentric LVH (HR: 2.35 [95%CI: 1.87-2.97]) and concentric LVH (HR: 4.35 [95%CI: 3.16-5.99], all p<0.001) were associated with cardiovascular mortality in univariate Cox models and in multivariate Cox models (HR: 1.89 [95%CI: 1.34-2.66], and HR: 2.72 [95%CI: 1.72-4.30], all p<0.001, respectively, Figure 2a).

When analyzing the 2 new subgroups each in eccentric and concentric LVH, cardiovascular death occurred in 56 (15%) with eccentric non-dilated, 41 (43%) with eccentric dilated, 41 (30%) with concentric non-dilated and 3 (38%) with concentric dilated LVH, respectively. In the eccentric group both non-dilated and dilated LVH predicted cardiovascular mortality in univariate analyses, but the later with a substantially higher risk of cardiovascular death (HR: 6.85 [95%CI: 4.80-9.75], p<0.001, vs. HR: 1.56 [95%CI: 1.17-2.08], p=0.003, respectively).

In a multivariate Cox model, dilated eccentric LVH, remained more strongly associated with cardiovascular death than non-dilated eccentric LVH (HR: 4.24 [95%CI: 2.27-7.89], p<0.001 vs. HR: 1.60 [95%CI: 1.09-2.34], p=0.016, respectively, Figure 2b). In the concentric group, both dilated and non-dilated groups were univariable predictors of cardiovascular death (HR: 4.24 [95%CI: 3.05-5.90] and HR: 8.04 [95%CI: 2.57-25.1], both p<0.001, respectively). In multivariate Cox models, both hazards remained increased, but because of the small number patients in dilated concentric LVH, only non-dilated concentric LVH remained significant associated with risk of cardiovascular death (HR: 2.73 [95%CI: 1.72-4.34], p<0.001 vs. HR: 2.54 [95%CI: 0.35-18.58], p=0.36, respectively, Figure 2b).

Sensitivity Analyses of Method of Indexation to Define Left Ventricular Hypertrophy or Increased Left Ventricular Volume in the 4-Group Classification System

The first sensitivity analysis used RWT >0.45 instead of LVM/EDV partition to define concentricity; 128 (4.0%) participants had eccentric non-dilated, 46 (1.5%) had eccentric dilated, 29 (0.9%) had concentric non-dilated, none had concentric dilated and 2,967 (93.6%) did not have LVH. Because none had concentric dilated LVH, we focused on the eccentric group. The same pattern of eccentric dilated LVH being substantially more associated with both endpoints persisted when using RWT to define concentricity instead of LVM/EDV. In multivariate Cox analysis, eccentric dilated LVH predicted both cardiovascular (HR: 3.92 [95% CI: 2.15-7.16], p<0.001 and all-cause mortality (HR: 2.43 [95% CI: 1.63-3.61], p<0.001); furthermore, eccentric non-dilated LVH predicted cardiovascular (HR: 1.98 [95%CI: 1.42-2.76], p<0.001) and all-cause mortality (HR: 1.55 [95%CI: 1.28-3.61], p<0.001) although less strong compared to eccentric dilated LVH defined using RWT criteria.

The second sensitivity analysis used LVM/BSA to define LVH instead of LVM/height$^{2.7}$; 133 participants (4.2%) had eccentric non-dilated, 83 (2.6%) had eccentric dilated, 96 (3.0%) had concentric non-dilated, 8 (0.3%) had concentric dilated LVH and 2,850 (89.9%) had

normal LVM. The majority of the key findings described above persisted when defining LVH by indexation for BSA instead of height[2,7]. In multivariate Cox models, eccentric non-dilated LVH was associated with all-cause (HR: 1.91 [95%CI: 1.49-2.46], p<0.001) and cardiovascular mortality (HR: 2.24 [95%CI: 1.45-3.46], p=0.003), and eccentric dilated LVH remained strongly associated with both cardiovascular and all-cause mortality and (respectively, HR: 3.86 [95%CI: 2.00-7.45], p<0.001 and HR: 2.50 [95%CI: 1.62-3.85], p<0.001).

## Discussion

For the first time, the ability of new 4-group system to classify LVH has been assessed, and compared to the established 2-group classification of LVH with respect to its ability to predict cardiovascular and all-cause mortality in a population-based sample. This study showed that when patients with eccentric LVH were divided into groups with normal or increased LV chamber volume, the later was associated with substantially higher risk of both all-cause and cardiovascular death. Subclassification of concentric LVH into groups with normal or increased LV chamber volume revealed similar higher risk of both all-cause and cardiovascular mortality in the dilated group compared to the non-dilated group. These results, showing consistently higher risk of death in dilated subgroups of eccentric and concentric LVH extents recently literature introducing a 4 group division of LVH by MRI [2] and showing its association with outcomes in a high-risk hypertensive population(mean baseline blood pressure 174±21 mmHg) echocardiography.[22]

The new 4-group model was developed as an alternative to the currently accepted 2-group classification system of LVH using MRI measurements in a population-based sample with relatively low burden of cardiovascular disease.[2] A recent analysis examining this model in high-risk hypertensive patients in the LIFE trial revealed significant differences among groups in hemodynamic and clinical characteristics despite similar baseline blood pressure.[23] There is a consistency in the literature suggesting concentric LVH is associated with poor outcome.[24, 25]

However, published studies report conflicting results on the association of eccentric LVH with outcome.[24, 26, 27] In the present study the new 4-group classification system of LVH revealed a substantially lower risk of all-cause and cardiovascular mortality in non-dilated LVH groups, which together with recent evidence of a low risk group among hypertensive patients with eccentric LVH without LV dilatation,[22] could partly explain the conflicting results on eccentric LVH.

It is controversial whether LV dilation is associated with cardiovascular events and mortality. Norton et al.[28] demonstrated that LV dilatation predicted heart failure in pressure overload hypertrophy, which might be caused by failure to compensate for the increased pressure. Supporting this, our group recently showed that LV dilatation with both eccentric and concentric LVH predicted greater morbidity and mortality than the non-dilated groups among hypertensive patients.[22] The present study revealed subgroups in eccentric and concentric LVH with dilated LV who had substantially higher risk of poor outcome among adults at high risk because of high presence of diabetes and obesity; but with normal or mild hypertension (mean blood pressure 130±21mmHg). Obesity is strongly related to diabetes and/or hypertension,[29] which has been shown to be associated with increased LVM and both systolic and diastolic dysfunction.[30] In addition, obesity per se has shown to be associated with myocardial apoptosis and cardiac dysfunction in rats;[31] and a nonmuscular component of myocardium in obesity is likely to be large, and formed of adipocytes and preadipocytes in addition to possibly large number of fibroblasts as shown in a autopsy study.[32] In the present study, participants had ~6 and ~4 times higher prevalence of diabetes compared to the Dallas Heart Study and the LIFE study, respectively. Diabetes has been shown to be associated with LV myocardial stiffening,[33] potentially explained by increased myocardial fibrosis.[34, 35] The higher prevalence of obesity and diabetes could easily be a confounder that might limit applicability of the 4 group model in these participants compared to groups with more purely hemodynamic stimuli to LVH. However, the consistency of poor outcome in the dilated subgroups of eccentric and concentric participants as in the LIFE study in the present study suggests that more

refined subdivision of LVH patterns may enhance prediction of prognosis from readily-available echocardiographic as well as cardiac MRI measurements.

Sensitivity Analyses Using Relative Wall Thickness or Left Ventricular Mass/body Surface Area

To verify that our findings were independent of indexation method we performed 2 sensitivity analyses comparing methods to identify increased concentricity. First, RWT was substituted for LVM/EDV to define concentricity which caused no one to be categorized with dilated concentric LVH. Secondly, LVM/BSA was used instead of LVM/ height$^{2.7}$ to define LVH. This approach only slightly changed the number of patients in the 4 groups. The consistency of these 2 alternative methods of indexation confirmed the finding that dilated eccentric LVH was associated with higher risk of all-cause and cardiovascular mortality compared to eccentric non-dilated LVH.

Limitations

A limitation of the present study was the small number of endpoints in some subgroups, limiting its power to verify incremental prognostic ability of the 4-group method in the 2 concentric groups of LVH, in particular when using RWT. However, we were still able to confirm significant differences in the two groups of greatest interest in our sensitivity analyses. In addition, our study was conducted in an American Indian population with high prevalence of diabetes and obesity; however, rising obesity and diabetes prevalence in other populations suggest that our findings may predict future results in other populations.

We did not investigate outcomes associated with concentric remodeling, which is not captured in the 4-group classification, despite its association with worse outcome compared to no LVH patients.[26, 36] However, in the present study no one of the non-LVH patients had concentric LV remodeling.

## Conclusion

In conclusion, this study showed that re-classifying LVH into 4 groups reveals differing cardiovascular and all-cause mortality in participants with high prevalence of diabetes and obesity. Verification of the enhanced prognostic power of the 4-subgroup classification of LVH in other populations is needed before recommending that this more complex approach replace the established subdivision of LVH into eccentric and concentric subgroups.

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## Table 1. Baseline Characteristics Stratified by Presence and Sub-Patterns of Left Ventricular Hypertrophy

| | | LVH | | | |
|---|---|---|---|---|---|
| | | Eccentric (n=472) | | Concentric (n=146) | |
| Variable | Normal LVM (n=2,560) | Non-dilated (n=376) | Dilated (n=96) | Non-dilated (n=138) | Dilated (n=8) |
| Age (years) | 59±8[a,d,g] | 61±8 | 63±8[c] | 63±8[c] | 66±5 |
| Male, % | 38.8%[a,g] | 25.8% | 41.7%[b] | 23.2%[a,e] | 12.5% |
| SBP (mmHg) | 128±19[a,d,g] | 136±20 | 141±27[c] | 149±27[a,e] | 164±23[a,e,i] |
| DBP (mmHg) | 74±10[f,g] | 76±10 | 72±11[c] | 78±11[a,d] | 81±11[f] |
| BMI (kg/m$^2$) | 30.4±5.8[a,f,g] | 35.2±6.8 | 29.2±5.1[a] | 32.6±6.1[a,d] | 31.4±4.4[i] |
| Diabetes, % | 45.5%[f,h] | 54.5% | 59.4%[c] | 76.8%[b] | 75.0% |
| Heart rate (min$^{-1}$) | 73±11[d] | 72±12 | 78±15[a] | 74±11[e,f] | 85±6[b,h] |
| eGFR (mL/min per 1.73m$^2$) [#] | 46[37;58][g] | 48[39;65] | 47[38;63] | 53[43;70][b,e] | 60[47;350][a,d,g] |
| HDL (mmol/l) | 1.1±0.4[i] | 1.1±0.3 | 1.0±0.3 | 1.0±0.3 | 1.0±0.4 |
| LDL (mmol/l) | 3.1±0.9[b,f] | 2.9±0.9 | 2.9±1.1 | 3.0±0.9 | 2.5±0.9 |
| Urine albumin/creatinine ratio (mg/mmol) [#] | 12[6;50][a,d,g] | 23[9;147] | 54[12;796][a] | 245[26;2,550][a,e] | 781[677;7,375][a,e,i] |
| High sensivity C-reactive protein | 1.3±1.0[a,e,h] | 1.7±1.0 | 1.6±1.1 | 1.6±1.0[c] | 2.4±1.4[c,f,i] |
| Calcium blockers, % | 8.7%[a,d,h] | 15.7% | 20.8% | 18.8% | 0% |
| Beta-blocker, % | 3.8% | 5.1% | 4.2% | 5.8%[c] | 0% |
| Ace-inhibitors, % | 14.1%[c,d,g] | 19.1% | 29.2% | 29.0% | 0% |
| Aspirin, % | 16.1%[d] | 18.9% | 31.3%[b,f] | 18.8%[f] | 0% |
| Anti-arrhythmics, % | 0.1%[b,d,h] | 2.7% | 29.2%[a] | 4.3%[d] | 37.5%[a,g] |
| Anticoagulant, % | 0.1%[d,i] | 1.1% | 7.3%[a] | 2.2% | 12.5%[b] |
| Diuretics, % | 10.2%[a,d,g] | 18.1% | 33.3%[b] | 26.8% | 25.0% |

Abbreviations: BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; HDL, high density lipoprotein; LVM, left ventricular mass; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

*For comparison among the 4 patterns of LVH.

†Based on logarithm transformed data.

[#]Median and interquatile range.

a) $p<0.001$ versus eccentric non-dilated.

b) $p<0.01$ versus eccentric non-dilated.

c) $p<0.05$ versus eccentric non-dilated.

d) $p<0.001$ versus eccentric dilated.

e) $p<0.01$ versus eccentric dilated.

f) $p<0.05$ versus eccentric dilated.

g) $p<0.001$ versus concentric non-dilated.

h) $p<0.01$ versus concentric non-dilated.

i) $p<0.05$ versus concentric non-dilated.

## Table 2. Baseline Echocardiographic Measures Stratified by Presence and Sub-Patterns of Left Ventricular Hypertrophy

| | | LVH | | | |
|---|---|---|---|---|---|
| | | Eccentric (n=472) | | Concentric (n=146) | |
| Variable | Normal LVM (n=2,560) | Non-dilated (n=376) | Dilated (n=96) | Non-dilated (n=138) | Dilated (n=8) |
| Relative wall thickness | 0.35±0.04[c,d,g] | 0.34±0.03 | 0.30±0.03[a] | 0.44±0.07[a,d] | 0.36±0.01[d,g] |
| Total peripheral resistance index by BSA (kdynes*sec*cm$^{-5}$*m$^2$) | 3.3±0.9[a,e] | 3.1±0.9 | 2.9±0.8 | 3.3±1.0[c,e] | 3.3±1.2 |
| Left atrial diameter (cm) | 3.5±0.5[a,d,g] | 3.8±0.5 | 4.1±0.7[a] | 3.8±0.5[d,f] | 4.0±0.4[h,g] |
| Left ventricular mass/BSA | 77±12[a,d,g] | 104±12 | 133±16[a] | 121±21[a,d] | 173±15[a,d,g] |
| Stroke volume (ml) | 71±12[a,d] | 86±17 | 81±23[a] | 72±14[a,d] | 72±17[c] |
| Cardiac output (L/min) | 4.7±1.1[a,d,i] | 5.3±1.2 | 5.2±1.4[a] | 4.9±1.1[a,d] | 5.2±1.1[a,h] |
| Ejection fraction (%) | 62±3[a,d,g] | 61±7 | 48±15[a] | 61±7[d] | 46±15[a,g] |
| Stress-Corrected Midwall shortening (%) | 105±12[c,d,g] | 104±15 | 88±22[a] | 88±15[a] | 75±15[a,f,h] |
| Segmental wall motion abnormalities, % | 4.7[a,d,g] | 9.8 | 46.9[a] | 13.0[c,d] | 87.5[a,f,g] |
| Concentricity (g/ml) | 1.4±0.2[g] | 1.5±0.1 | 1.4±0.2 | 2.0±0.4 | 1.9±0.2 |
| Left ventricular mass/height$^{2.7}$ | 38±6 | 56±5 | 67±11 | 62±10 | 90±10 |
| Mitral valve E/A ratio[#] | 0.9±0.3[d,g] | 0.9±0.3 | 1.2±0.4[a] | 0.8±0.3[c,d] | 1.1±0.5[h] |

Abbreviations: BSA, body surface area; LVM, left ventricular mass; LVH, left ventricular hypertrophy.

*For comparison among the 4 patterns of LVH.

†Based on logarithm transformed data.

[#]Mean and interquatile range.

a) p<0.001 versus eccentric non-dilated.

b) p<0.01 versus eccentric non-dilated.

c) p<0.05 versus eccentric non-dilated.

d) p<0.001 versus eccentric dilated.

e) p<0.01 versus eccentric dilated.

f) p<0.05 versus eccentric dilated.

g) p<0.001 versus concentric non-dilated.

h) p<0.01 versus concentric non-dilated.

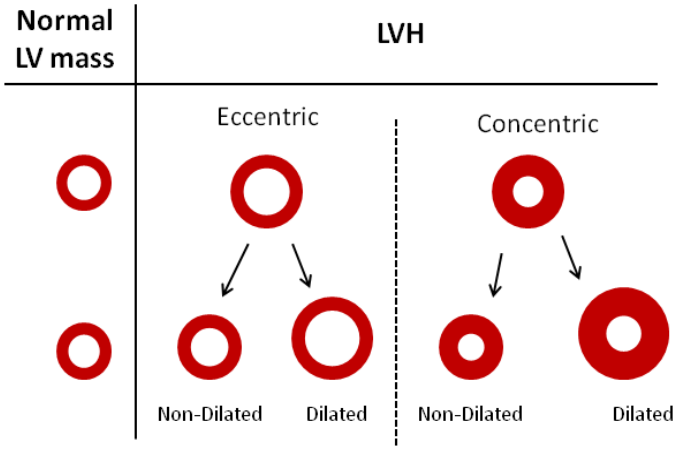
i) p<0.05 versus concentric non-dilated.

## Table 3. Outcomes in the 4 geometric groups

| | | LVH | | | |
|---|---|---|---|---|---|
| | | Eccentric (n=472) | | Concentric (n=146) | |
| Variable | Normal left ventricular mass (n=2,560) | Non-dilated (n=376) | Dilated (n=96) | Non-dilated (n=138) | Dilated (n=8) |
| All-cause mortality, n (%; %/year) | 872 (34%; 0.03%/year) | 158 (42%;0.04%/year) | 76 (79%; 0.12%/year) | 102 (74%; 0.9%/year) | 6 (75%; 0.13%/year) |
| Cardiovascular mortality, n (%; %/year) | 262 (10%; 0.01%/year) | 56 (15%; 0.01%/year) | 41 (7%; 0.06%/year) | 41 (30%; 0.4%/year) | 3 (38%; 0.06%/year) |

Abbreviations: LVH, left ventricular hypertrophy.

**Figure 1 & Central Illustration. Graphic Illustration of the 4 Left Ventricular Hypertrophy Patterns**

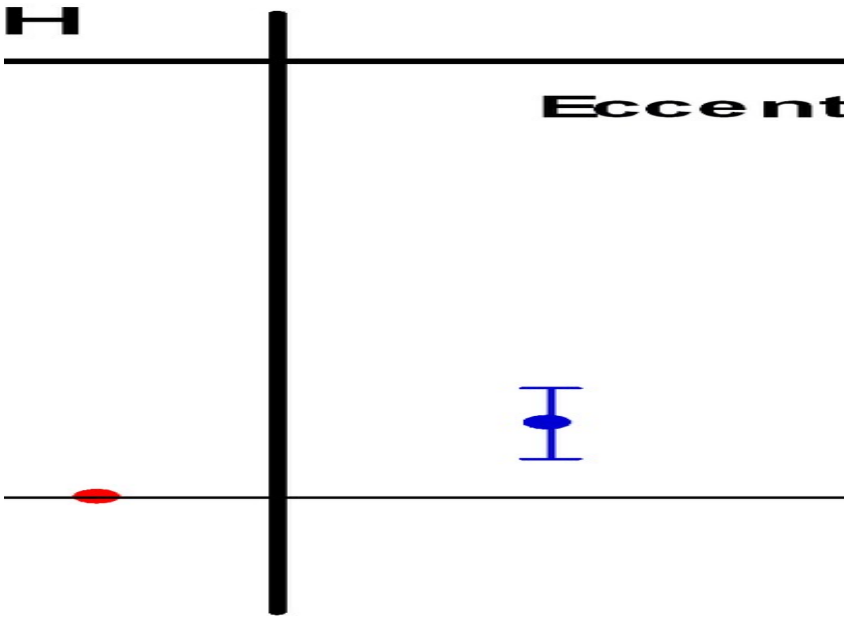



| | | | | | |
|---|---|---|---|---|---|
| **Patients, n(%):** | 2,560 (81.6%) | 376 (11.8%) | 96 (3.1%) | 138 (4.3%) | 8 (0.3%) |
| Increased LV mass/height$^{2.7}$ *[≥50g/m$^{2.7}$ (women and men)]* | – | + | + | + | + |
| Increased concentricity (LVM/LVEDV) *[≥1.07g/mL (women) and ≥1.08g/mL (men)]* | NA | – | – | + | + |
| Increased LVEDV/BSA *[LVEDV/BSA: ≥85mL/m$^2$]* | NA | – | + | – | + |

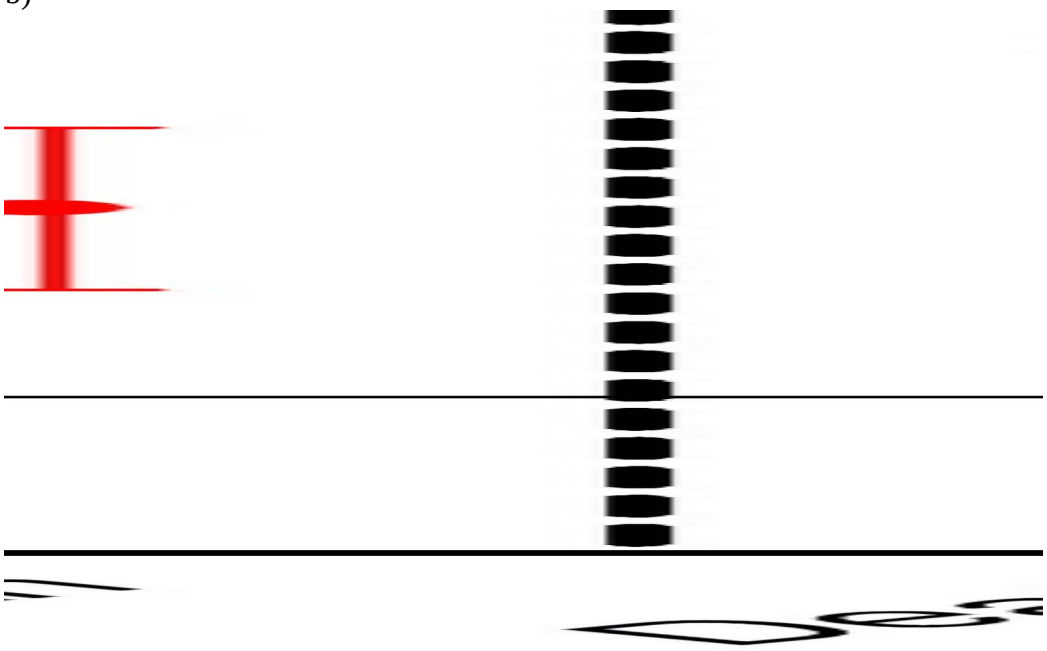
Abbreviations: BSA, body surface area; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVH, left ventricular hypertrophy; LVM, left ventricular mass.

**Figure 2. Hazard Ratio and Confidence Interval from Multivariable Cox models for Cardiovascular Mortality and All-Cause Mortality in Panel A 2- and Panel B 4-Left Ventricular Hypertrophy Classification model**

a)

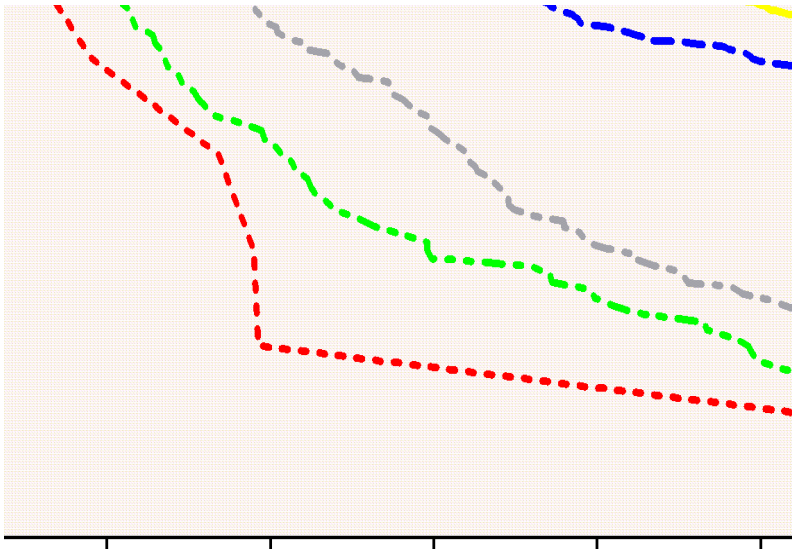



b)



Abbreviations: CV, cardiovascular; LVH, left ventricular hypertrophy.

**Figure 3. Survival by Left Ventricular Geometric Patterns**



Abbreviations: LV, left ventricular.