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# Left ventricular hypertrophy reclassification and death: application of the Recommendation of the American Society of Echocardiography/ European Association of Echocardiography†

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**Aims** Despite the American Society of Echocardiography (ASE)/European Association of Echocardiography (EAE) recommended the use of left ventricular (LV) mass to diagnose left ventricular hypertrophy (LVH), several laboratories continue to use only the septal thickness by M-mode because it appears easier to measure. Aim of the study was to investigate the discrepancy between the categorization of LVH severity based on measurement of septal thickness and indexed LV mass and the relative prognostic utility of these two methods.

**Methods and results** Observational cohort study. Unselected adults (>18 years) referred to the echocardiography laboratory for any indication had septal thickness and LV mass measured by the ASE/EAE formula using LV linear dimensions indexed to body surface area. LVH was categorized as absent, mild, moderate, and severe according to the ASE/EAE guideline sex-specific categorization cut-offs for septal thickness and LV mass. Follow-up for death was obtained from the national death index. A total of 2545 subjects (mean age 61.9 $\pm$ 15.8, 53% women, mean diastolic septal thickness 10.3 $\pm$ 2.2 mm, and mean indexed LV mass 107.5 $\pm$ 37.3 g/m$^2$) were enrolled. Agreement between the two methods in classifying LVH degree across the four categories was 52.6% (Kappa = 0.29, 95% confidence interval (CI): 0.26–0.32, $P < 0.001$). Of the 2513 subjects without severely thickened septum, 472 (18.9%) had severely abnormal indexed LV mass. Vice versa, of the 2045 individuals without severely abnormal indexed LV mass, only 4 (0.1%) were classified as severe LVH by septal thickness. After a mean follow-up of 2.5 $\pm$ 1.2 years 121 (4.7%) deaths occurred. Using indexed LV mass partition values there was a graded association between LVH degree and survival. Compared with patients with normal indexed LV mass, the adjusted hazard ratio (HR) for death from all causes was 2.17 for mild (95% CI: 1.23–3.81, $P = 0.007$), 3.04 for moderate (95% CI: 1.76–5.24, $P < 0.001$), and 3.81 for severe (95% CI: 2.43–5.97, $P < 0.001$) LVH by indexed LV mass. The area under the receiver-operator characteristic (ROC) curve for the four degrees of LVH by indexed LV mass was superior [area under the curve (AUC) = 0.66] to that of the septal thickness partition values (AUC = 0.58, $P = 0.0004$).

**Conclusion** In a large cohort study of unselected adult outpatients referred to the echocardiography laboratory, the measurements of indexed LV mass applying the ASE/EAE recommended cut-offs yielded remarkable discrepancy in the diagnosis of LVH severity and offered prognostic information beyond that provided by septal thickness only criteria.

**Keywords** Left ventricular hypertrophy • Septal wall thickness • Indexed left ventricular mass • Prognosis

†Application of the Recommendation of the American Society of Echocardiography/European Association of Echocardiography.

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# Introduction

Previous studies reported that marked discrepancies between the echocardiographic measurement of left ventricular (LV) wall thickness and LV mass leading to uncertainty regarding the actual echocardiographic diagnosis of left ventricular hypertrophy (LVH).[1] The American Society of Echocardiography (ASE)/European Association of Echocardiography (EAE) guidelines for chamber quantification[2] proposed sex-specific cut-offs to categorize the degree of LVH based on the distribution of LV mass and wall thickness in relation to reference limits in a ethnically heterogeneous North-American population.[3] These ASE/EAE guidelines concluded that LV mass from the ASE-recommended formula using LV linear dimensions indexed to body surface area (BSA) is preferred in the diagnosis of LVH over linear measurements such as septal or posterior wall thickness since it provides a more accurate and reproducible estimation of LV mass, when compared with reference standards such as autoptic studies.[4,5] Nonetheless, several laboratories continue to use only the septal thickness by M-mode to evaluate the LVH because it appears easier to measure.

To the best of our knowledge, there are no studies concurrently assessing the traditionally measured LV septal thickness by M-mode and the LV mass as an estimate of LVH applying the recently published cut-offs. For these reasons, we sought to determine, in a large group of unselected outpatients referred to a tertiary care echocardiography laboratory, whether sex-specific categorization of LV mass based on the ASE-recommended cut-offs resulted in diagnostic and prognostic reclassification then if only the septal wall thickness by M-mode were used.

# Methods

The study population comprised unselected elective adult outpatients who underwent standard Doppler echocardiography for any indication in the period from January 2005 to March 2009 at the echocardiography laboratory of Modena University Hospital. Criteria for enrolment were: (i) age $\geq$18 years; (ii) complete resting two-dimensional echocardiogram including prospective real-time measurement of LV mass; (iii) residency in Modena province, Italy. For patients undergoing more than one echocardiographic exam during the aforementioned time frame, we considered only the first access to the echocardiography laboratory.

## Echocardiographic data

All exams were performed using Acuson Sequoia ultrasound system, Siemens Medical Solutions, Mountain View, California and were performed and/or supervised by cardiologists fully trained in echocardiography with long-standing experience with the technique and intense hands-on training period with interpretation of >750 studies.[6]

The LV diameters were measured from 2D-guided M-mode method in the parasternal short-axis view. LV end-diastolic dimensions were measured at the onset of the QRS complex. The LV volumes were derived according to the modified biplane Simpson's method in the apical four- and two-chamber views. The LV ejection fraction was calculated in the standard fashion from LV end-diastolic and end-systolic volume.[7]

Regional LV function was assessed with a standard 16-segment model.[2] Segmental scores were assigned as follows: normal or hyperkinesis = 1; hypokinesis = 2; akinesis = 3; dyskinesis = 4; and aneurismal = 5. The LV wall motion score index was derived as the sum of all scores divided by the number of segments visualized.

Left atrial volume was assessed by the modified biplane Simpson's method from apical four- and two-chamber views an indexed to BSA. Measurements were obtained in end-systole from the frame preceding mitral valve opening.[8] Individual echocardiographic Doppler parameters (mitral inflow pattern, tissue Doppler, and Valsalva manoeuver where necessary) were integrated to grade diastolic function in four stages: normal diastolic function; impaired relaxation with normal or near-normal filling pressures (grade I/IV); impaired relaxation with moderate elevation of filling pressures, pseudonormal filling (grade II/IV); and impaired relaxation with marked elevation of filling pressures, restrictive filling (grades III–IV/IV) as previously described.[9]

Each value represented the average of three consecutive beats. Significant left side valve disease severity was defined as the presence of aortic or mitral prosthesis or the presence of greater than moderate native mitral or aortic valve stenosis or insufficiency, similarly to previous reports.[10] Valve disease severity was defined according to the American Heart Association/American College of Cardiology guidelines for the management of valvular heart disease.[11] By applying these guidelines, the cardiologist performing the exam graded valve disease as absent, mild, moderate, and severe and this information was embedded in the echo report. The methods used included pulsed wave and continuous wave Doppler velocities and gradients, direct measurement of valve area planimetry, continuity equation, colour Doppler to assess the jet width, or proximal isovelocity surface area for quantitative evaluation. The method/s used to classify valve disease severity was at the discretion of the physician performing the exam and often the final judgment was based on the combination of more than one method. Valve disease severity was defined according to the American Heart Association/American College of Cardiology guidelines for the management of valvular heart disease. Patients with greater than moderate valvular heart disease were considered having significant valvular disease.

All measurements were performed online and immediately entered in an electronic database at the time of the echocardiogram; no modification from the original database was applied and no measurement was made off line. Hence, the study consisted in a retrospective analysis of data prospectively entered in the electronic echocardiographic database.

## Echocardiographically determined left ventricular mass

The ASE-recommended formula for estimation of LV mass from LV linear dimensions based on modelling the LV as a prolate ellipse of revolution. LV mass was calculated thus: LV mass = $0.8[1.04(\text{LVIDD} + \text{IVST} + \text{PWT})^3 - (\text{LVIDD})^3] + 0.6$, where LVIDD represents LV end-diastolic internal dimension and IVST and PWT indicate the end-diastolic thicknesses of the interventricular septum and LV posterior wall, respectively.[5] LV mass were indexed to BSA.

## Cut-off limits for left ventricular hypertrophy

The ASE/EAE guidelines suggest the following cut-offs for LVH: LV septal wall thickness >0.9 cm for women and >1.0 cm for men, LV mass/BSA >95 g/m$^2$ for women and LV mass/BSA >115 g/m$^2$ for men. Furthermore, the ASE/EAE guidelines subdivided on an ordinal scale the values exceeding the reference limits to identify patients with mild LVH (LV septal thickness 1.0–1.2 cm, LV mass/BSA 96–108 g/m$^2$ for women and LV septal thickness 1.1–1.3 cm, LV mass/BSA 116–131 g/m$^2$ for men), moderate LVH (LV septal thickness

1.3–1.5 cm, LV mass/BSA 109–121 g/m$^2$ for women and LV septal thickness 1.4–1.5 cm, LV mass/BSA 132–148 g/m$^2$ for men) and severe LVH (LV septal thickness 1.6 cm, LV mass/BSA ≥122 g/m$^2$ for women and LV septal thickness ≥1.7 cm, LV mass/BSA ≥149 g/m$^2$ for men).[2]

## Left ventricular geometry

The relative wall thickness (RWT) were measured by the formula (2×PWTd)/LVIDd which permitted the categorization of an increase in LV mass as either concentric (RWT ≥0.42) or eccentric (RWT <0.42) hypertrophy[1] and allowed the identification of concentric remodelling (normal LV mass with increased RWT).

## Clinical data

Age, sex, height, weight, BSA, body mass index, and cardiac rhythm were recorded at the time of the echocardiogram and entered in the electronic echocardiography report. Prior history of cardiovascular diseases (prior acute coronary syndromes—including ST elevation myocardial infarction and unstable angina/non-ST elevation myocardial infarction; history of chronic coronary artery disease; prior acute or chronic heart failure; and prior stroke) was obtained using the hospital discharge codes of public hospitals of Modena province. Risk factors were obtained retrospectively by manual review of electronic clinical notes of the public hospitals of the province. These electronic records allow assessment of outpatient visits as well as hospital discharge notes.

To collect information on medications, we combined two methods: (i) we retrospectively reviewed through the electronic databases of Modena Province public hospital discharge letters and ambulatory cardiology visits; (ii) we used the Emilia Romagna Region pharmacy centralized electronic database. This electronic database contains all prescriptions that are filled in all pharmacies of the region by all residents regardless of who is the physician prescribing the medication. We examined all prescriptions filled in 60 days before and 30 days after the date of the exam.

## Follow-up

All cause death was the endpoint of the study. Follow-up information for death was obtained from the national death index, where the status of all citizens is steadily constantly updated and is 100% complete. Indeed in Italy it is mandatory by law that all deceased patients are immediately registered in this national data bank.

Data are presented as frequency or mean ± standard deviation. To measure the strength of the relation between the septal thickness and indexed LV mass Pearson's correlation coefficients ($r$) was calculated. The Kappa and Weighted Kappa statistics were used to calculate the strength of the accord in categorizing the presence and the degree of LVH of the two methods.[12] The per cent of agreement was calculated as the ratio between agreed-on measures and the total.

## Statistical analysis

Kaplan–Meier curves were constructed to show survival according to LVH degrees and groups were compared with the log rank test considering a linear trend across the levels. Univariate and multivariable Cox proportional hazards models were used to assess the association between LVH degrees and the risk of death, the risk was presented as hazard ratio (HR) and 95% confidence interval (CI).

Receiver-operator characteristic (ROC) curves were generated to assess the overall performance for death prediction of septal thickness and indexed LV mass both as continuous variables as well as using guideline proposed partition values. The area under the curve (AUC) of the ROC curves were compared using the DeLong method.

All tests were two-tailed. A $P < 0.05$ indicated statistical significance. All analyses were performed using SPSS (Chicago, IL, USA) version 15.0 for Windows and MedCalc 11.5.0.

**Table 1 Baseline characteristics of the patients included in the study**

| | Total, $n = 2545$ |
|---|---|
| Baseline clinical characteristics (%) | |
| Age, years | 61.9 ± 15.8 |
| Women | 1434 (53) |
| BSA, m$^2$ | 1.82 ± 0.22 |
| BMI, m/kg$^2$ | 26.2 ± 4.6 |
| Hypertension, $n$[a] | 1325 (71.6) |
| Diabetes mellitus, $n$[a] | 228 (12.3) |
| Hyperlipidaemia, $n$[a] | 444 (24.0) |
| Smoking status, $n$[a] | 187 (10.1) |
| Prior acute coronary syndrome | 230 (9.0) |
| History of chronic/stable coronary artery disease | 309 (12.1) |
| History of heart failure | 208 (8.2) |
| Prior stroke | 42 (1.7) |
| Significant valvular heart disease | 274 (10.8) |
| Atrial fibrillation | 196 (7.7) |
| Echocardiographic characteristics | |
| LVEF, % | 64.6 ± 12.2 |
| WMSI | 1.07 ± 0.24 |
| LAVi, mL/m$^2$, $n$[b] | 34.7 ± 17.0 |
| Mass indexed, g/m$^2$ | 107.5 ± 37.3 |
| Relative wall thickness | 0.40 ± 0.09 |
| Relative wall thickness >0.42 (%) | 1007 (39.6) |
| Medications (%) | 440 (17.3) |
| Antiplatelets | 469 (18.4) |
| Beta-blockers | 333 (13.1) |
| Diuretics | 262 (10.3) |
| Calcium channel blockers | 741 (29.1) |
| ACE inhibitors/angiotensin receptor blockers | 327 (12.8) |
| Statins | 2 (0.1) |
| Anti-arrhythmics (class IA, IB) | 26 (1.0) |
| Anti-arrhythmics (class IC) | 18 (0.7) |
| Amiodarone | 117 (4.6) |
| Insulin/oral hypoglycaemic drugs | 174 (6.8) |
| Anticoagulants | 440 (17.3) |

BSA, body surface area; BMI, body mass index; LVEF, left ventricular ejection fraction; WMSI, wall motion score index; LAVi, left atrium volume indexed.
[a]$n = 1851$.
[b]$n = 1624$.

# Results

During the study period, 2545 subjects (mean age 61.9 ± 15.8, 53% women) met the inclusion criteria, and were considered for the analysis. Characteristics of the patients included in the study are summarized in *Table 1*.

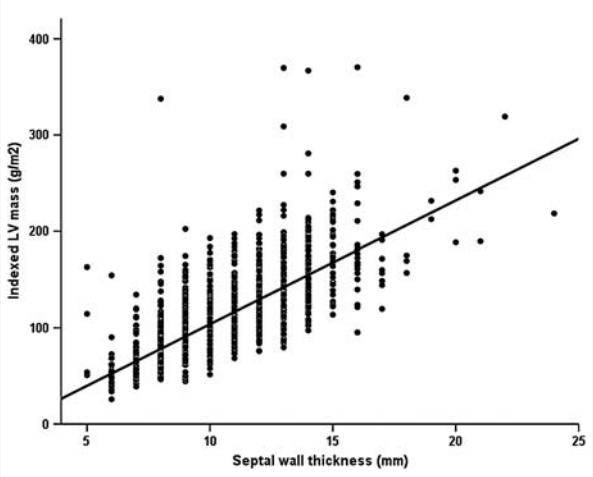


**Figure 1** Correlation between left ventricular septal diastolic thickness and indexed left ventricular mass. Regression line is shown as solid line.

**Table 2 Agreement between septal thickness and indexed left ventricular mass in classifying left ventricular hypertrophy**

| | Normal LV by indexed LV mass, $n = 1347$ (52.9%) | Hypertrophy by indexed LV mass, $n = 1198$ (47.1%) |
|---|---|---|
| Normal by septal thickness, $n = 1210$ (47.5%) | 1018 (40.0%) | 192 (7.5%) |
| Hypertrophy by septal thickness, $n = 1335$ (52.5%) | 329 (12.9%) | 1006 (39.5%) |

Among all subjects enrolled mean LV mass was 195.6 + 72.2 g and mean indexed LV massed to BSA was 107.5 + 37.3 g/m$^2$. Mean septal diastolic thickness was 10.3 + 2.2 mm. There was a significant positive correlation between septal thickness and LV indexed mass ($r = 0.75$, $r^2 = 0.57$, $P < 0.001$) but a large scatter was observed (*Figure 1*).

## Reclassification of left ventricular hypertrophy

According to the ASE/EAE guideline cut-offs, 1335 (52.5%) subjects were classified as having LVH when the septal thickness was used and 1198 (47.1%) by indexed LV mass. The observed proportion of overall agreement between the two methods in classifying LVH was 79.5%, with a similar proportion of positive and negative agreement (Kappa = 0.592, 95%CI: 0.560–0.623, $P <$ 0.001), indicating moderate agreement. Accordingly, in about one of five subjects there was a discordance between the two definitions in classifying LVH. Particularly, of 1210 subjects with normal septal thickness, 192 (15.9%, 7.5% of total) were reclassified as LVH by indexed LV mass. Vice versa, of the 1347 with normal indexed LV mass, 329/1347 (24.4%, 12.9% of total) had LVH by the septal thickness only criterion (*Table 2*). Patients in whom LVH was identified by only one criterion were not significantly different from those who classified having LVH by both criteria, except for a higher prevalence of diabetes mellitus (*Table 3*).

## Reclassification of left ventricular hypertrophy severity

There was a different distribution of LVH severity by using septal thickness and indexed LV mass partition values (*Figure 2*). Using septal thickness partition values, LVH was classified as mild in 1069 (42%), moderate in 234 (9.2%), and severe in 32 (1.2%) subjects while using indexed LV mass it was categorized as mild in 391 (15.4%), moderate in 307 (12.1%), and severe in 500 (19.6%) patients ($P < 0.001$).

Agreement in classifying LVH degree using the two methods was met in 1340 subjects and the proportion of overall agreement across the four categories was 52.6%. Kappa was 0.29 (95% CI: 0.265–0.323, $P < 0.001$) indicating fair agreement (*Table 4*). Considering the close matches, the weighted Kappa was 0.41, which indicates a moderate agreement. The interclass correlation was 0.52 (95% CI: 0.42–0.60, $P < 0.001$).

Of the 2513 subjects without severely thickened septum, 472 (18.9%) had severely abnormal indexed LV mass. Conversely, of the 2045 individuals without severely abnormal indexed LV mass only 4 (0.1%) were classified as severely hypertrophic by septal thickness.

## Mortality and left ventricular hypertrophy reclassification

After a mean follow-up of 2.5 ± 1.2 years 121 (4.7%) deaths occurred. Survival was worse with greater LVH. Using septal thickness partition values 3-year survival was 96.6 ± 0.6% among patients without LVH, 93.4 ± 1.0% among those with mild, 92.0 ± 2.4% among those with moderate, and 93.8 ± 4.3 among those with severe LVH ($P$ for trend <0.001, $\chi^2$ of the model 13.2, *Figure 3*). Compared with patients with normal septal thickness those with mildly abnormal septal thickness had a 1.7 (95% CI: 1.14–2.54, $P = 0.009$) increased risk of death, those with moderately abnormal septal thickness had a 2.33 (95% CI: 1.34–4.06, $P = 0.003$) increased risk and those with severely abnormal septal thickness had a 3.00 (95% CI: 0.92–9.71, $P = 0.06$) increased risk.

Using indexed LV mass partition values, there was a graded association between LVH degree and survival, at 3 years survival was 97.4 ± 0.5% among subjects with normal indexed LV mass, 94.3% ± 1.5 among those with mild LVH, 91.5 ± 2.0% among those with moderate, 90.9 ± 1.5% among those with severe LVH ($P$ for trend <0.001, $\chi^2$ 40.0 of the model, *Figure 4*).

Compared with patients with normal indexed LV mass those with mildly abnormal LV mass had a 2.17 (95% CI: 1.23–3.81, $P = 0.007$) increased risk of death, those with moderately abnormal indexed LV mass had a 3.04 (95% CI: 1.76–5.24, $P < 0.001$) increased risk, and those with severely abnormal indexed LV

**Table 3 Baseline characteristics according to the discrepancy in left ventricular hypertrophy categorization. Abbreviations as in Table 1**

| | LVH by LV mass and septal thickness, *n* = 1006 | LVH by septal thickness only, *n* = 329 | LVH by LV mass only, *n* = 192 | *P*-value |
|---|---|---|---|---|
| Baseline characteristics | | | | |
| Age | 62.2 ± 5.6 | 62.3 ± 15.9 | 62.3 ± 14.5 | 0.989 |
| Women (%) | 572 (56.9) | 183 (55.6) | 97 (50.5) | 0.268 |
| BSA, $m^2$ | 1.82 ± 0.22 | 1.82 ± 0.21 | 1.84 ± 0.23 | 0.756 |
| BMI, $kg/m^2$ | 26.3 ± 4.7 | 26.2 ± 4.7 | 26.1 ± 4.5 | 0.840 |
| Hypertension[a] (%) | 538 (72.9) | 167 (68.4) | 104 (75.9) | 0.242 |
| Diabetes mellitus[a] (%) | 82 (11.1) | 44 (18.0) | 26 (19.0) | 0.003 |
| Hyperlipidaemia[a] (%) | 183 (24.8) | 60 (24.6) | 38 (27.7) | 0.750 |
| Smoking status[a] (%) | 72 (9.8) | 27 (11.0) | 19 (13.9) | 0.521 |
| Prior acute coronary syndrome (%) | 99 (9.8) | 32 (9.7) | 32 (12.0) | 0.646 |
| History of chronic/stable coronary artery disease (%) | 131 (13.0) | 38 (11.6) | 25 (13.0) | 0.777 |
| History of heart failure (%) | 85 (8.4) | 28 (8.5) | 16 (8.3) | 0.998 |
| Prior stroke (%) | 16 (1.6) | 10 (3.0) | 1 (0.5) | 0.084 |
| Significant valvular heart disease (%) | 108 (10.7) | 32 (9.7) | 21 (10.9) | 0.859 |
| Atrial fibrillation (%) | 81 (8.1) | 20 (6.1) | 18 (9.4) | 0.349 |
| Echocardiographic characteristics | | | | |
| LVEF, % | 64.9 ± 12.1 | 62.2 ± 12.8 | 64.8 ± 13.3 | 0.706 |
| WMSI | 1.07 ± 0.23 | 1.07 ± 0.24 | 1.09 ± 0.29 | 0.486 |
| LAVi, $mL/m^2$[b] | 34.2 ± 17.1 | 34.7 ± 16.1 | 35.4 ± 16.4 | 0.772 |
| LV mass, $g/m^2$ | 107.5 ± 36.6 | 109.7 ± 41.7 | 111.2 ± 39.7 | 0.735 |
| Relative wall thickness | 0.40 ± 0.09 | 0.41 ± 0.09 | 0.40 ± 0.09 | 0.127 |
| Relative wall thickness >0.42 (%) | 404 (40.2) | 149 (45.3) | 72 (37.5) | 0.152 |

BSA, body surface area; BMI, body mass index; LVEF, left ventricular ejection fraction; WMSI, wall motion score index; LAVi, left atrium volume indexed.
[a]*n* = 1851.
[b]*n* = 1624.

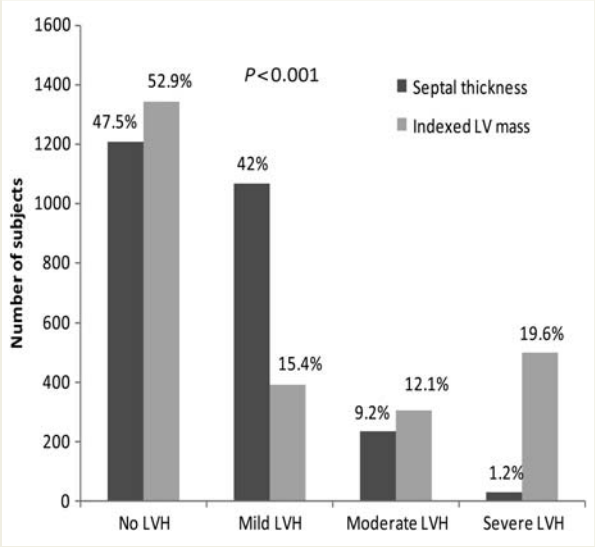


**Figure 2** Distribution of left ventricular hypertrophy severity by using septal thickness and indexed mass partition values.

mass had a 3.81 (95% CI: 2.43–5.97, $P < 0.001$) increased risk. Considering death as dependent variable, the area under the ROC curve for the four degrees of LVH by indexed LV mass was superior (AUC = 0.66, 95% CI: 0.64–0.68) to that based on the septal thickness partition values (AUC = 0.58, 95% CI: 0.56–0.60), $P = 0.0004$. Similarly, the AUC was 0.71 (95% CI: 0.69–0.73) for indexed LV mass and 0.61 (95% CI: 0.60–0.63) for septal thickness both considered as continuous variables, $P < 0.0001$.

At multivariable analyses, after adjusting for age, gender, LV ejection fraction, atrial fibrillation, presence of significant valvular heart disease, and LV wall motion score index, indexed LV mass partition values retained a significant association with death, whereas LV septal thickness cut-offs were no longer significant (*Table 5*).

When both LVH definitions were entered in the multivariable model only indexed LV mass-based partition values retained statistically significant association with death during the follow-up (compared with normals HR 1.80, 95% CI: 0.97–3.31, $P = 0.060$ for mildly abnormal indexed LV mass, HR: 2.3, 95% CI: 1.25–4.22, $P = 0.007$ for moderately abnormal indexed LV mass and HR: 2.38, 95% CI: 1.27–4.44, $P = 0.007$ for severely abnormal indexed LV mass).

**Table 4 Agreement between septal thickness and indexed left ventricular mass in classifying left ventricular hypertrophy severity**

| | No hypertrophy by mass, $n = 1347$ (52.9%) | Mild hypertrophy by mass, $n = 391$ (15.4%) | Moderate hypertrophy by mass, $n = 307$ (12.1%) | Severe hypertrophy by mass, $n = 500$ (19.6%) |
|---|---|---|---|---|
| No hypertrophy by septal thickness, $n = 1210$ (47.5%) | 1018 (40%) | 103 (4.0%) | 45 (1.7%) | 44 (1.7%) |
| Mild hypertrophy by septal thickness, $n = 1069$ (42.0%) | 317 (12.4%) | 267 (10.5%) | 232 (9.1%) | 253 (9.9%) |
| Moderate hypertrophy by septal thickness, $n = 234$ (9.2%) | 12 (0.4%) | 20 (0.7%) | 27 (1.0%) | 175 (6.8%) |
| Severe hypertrophy by septal thickness, $n = 32$ (1.2%) | 0 | 1 | 3 (0.1%) | 28 (1.1%) |

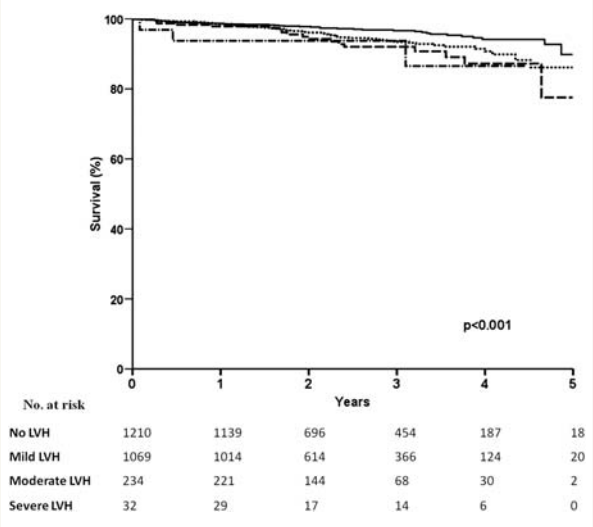


**Figure 3** Survival according to left ventricular septal thickness partition values proposed by the American Society of Echocardiography/European Association of Echocardiography classification scheme. Solid black line indicates patients without hypertrophy; dotted line, mild hypertrophy; dashed line, moderate hypertrophy; dash-dotted line, severe hypertrophy.

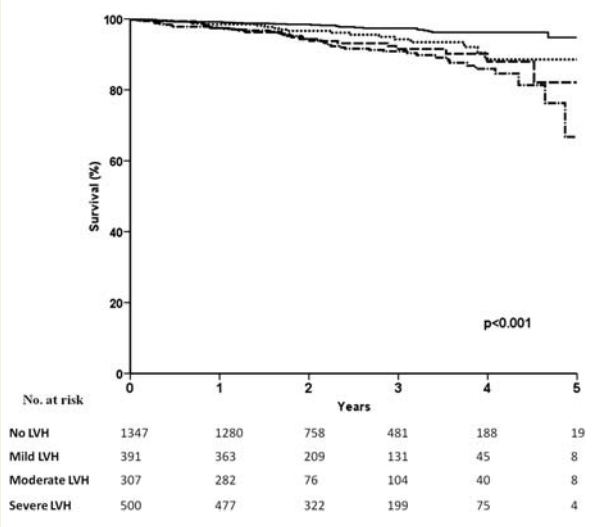


**Figure 4** Survival according to left ventricular mass partition values proposed by the American Society of Echocardiography/European Association of Echocardiography classification scheme. Solid black line indicates patients without LV hypertrophy; dotted line, dashed hypertrophy; dashed line, moderate hypertrophy; dash-dotted line, severe hypertrophy.

After further adjustment for prior history of acute coronary syndrome, history of chronic coronary artery disease, history of heart failure, prior stroke, and medications use (antiplatelets, anticoagulants, beta-blockers, calcium channel blockers, ACE inhibitors/angiotensin receptor blockers, diuretics, statins, amiodarone, other class antiahrrythmics, and insulin/oral hypoglycaemic drugs) the association between indexed LV mass partition values and death remained significant (compared with subjects without LVH, HR: 1.65, 95% CI: 0.93–2.93, $P = 0.085$ for mildly abnormal indexed LV mass, HR: 2.12, 95% CI: 1.21–3.70, $P = 0.008$ for moderately abnormal indexed LV mass and 2.17, 95% CI: 1.31–3.58, $P = 0.003$ for severely abnormal indexed LV mass).

Furthermore, after adjustment for cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia, and smoking) the results were similar. Interaction for gender and cardiac rhythm were not significant.

## Discussion

The main finding of the present study was that estimation of indexed LV massed by sex and BSA while applying the ASE/EAE linear recommended formula and cut-offs allowed identification of a significant number of patients with echocardiographic diagnosis of moderate or severe LVH that would have been missed if

**Table 5 Multivariable regression analysis for death using partition values of left ventricular hypertrophy based on septal thickness and indexed left ventricular mass**

| LV mass | HR (95% CI) | *P* of trend | Septal thickness | HR (95% CI) | *P*-value |
|---|---|---|---|---|---|
| No LVH | 1 | | No LVH | 1 | |
| Mild LVH | 1.82 (1.03–3.20) | 0.040 | Mild LVH | 1.52 (1.01–2.81) | 0.44 |
| Moderate LVH | 2.31 (1.33–4.01) | 0.003 | Moderate LVH | 1.44 (0.81–2.55) | 0.217 |
| Severe LVH | 2.30 (1.39–3.79) | <0.001 | Severe LVH | 1.91 (0.58–6.28) | 0.287 |
| Age | 1.02 (1.00–1.03) | 0.007 | Age | 1.02 (1.01–1.03) | 0.004 |
| Gender | 0.63 (0.43–0.92) | 0.016 | Gender | 0.68 (0.47–0.99) | 0.043 |
| Atrial fibrillation | 1.06 (0.63–1.81) | 0.821 | Atrial fibrillation | 1.07 (0.63–1.83) | 0.80 |
| EF | 0.99 (0.98–1.01) | 0.250 | EF | 0.99 (0.97–1.00) | 0.140 |
| Significant valvular disease | 2.78 (1.85–4.19) | <0.001 | Significant valvular disease | 3.21 (2.13–4.84) | <0.001 |
| WMSI | 1.52 (0.89–2.58) | 0.121 | WMSI | 1.74 (1.05–2.90) | 0.03 |

BSA, body surface area; BMI, body mass index; LVEF, left ventricular ejection fraction; WMSI, wall motion score index; LAVi, left atrium volume indexed.

classified only by septal thickness cut-offs. The fact that indexed LV mass partition values represented a more sensitive risk marker of death than septal thickness in our population reinforces these findings.

## Reclassification of echocardiographic diagnosis of left ventricular hypertrophy

Prevalence estimates of echocardiographic LVH are closely dependent on the criteria used. In a large study population of patients with moderate to severe hypertension, the echocardiographic diagnosis of LVH was present in 42–77% depending on the method of indexation and the partition value used.[13]

In the present study, we have demonstrated that septal thickness is often an unreliable approximation of the indexed LV mass, despite a statistically significant linear correlation between these two parameters. Of note, the proportion of subjects with LVH was similar using indexed LV mass and wall thickness criteria, but the agreement between the two methods was only modest (kappa = 0.59). Furthermore, indexed LV mass varied greatly among patients with a similar degree of LV septal thickness. Indeed, when the septal wall thickness measurements were used, only about 80% of the cases were classified correctly, whereas the remainders were misclassified.

Our result confirms and extends previous findings. Devereux *et al.*[1] demonstrated in a heterogeneous population with moderate or severe hypertension, mitral regurgitation, or dilated cardiomyopathy that indexed LV mass was abnormal in 73% while posterior wall thickness, septal thickness, and relative wall thickness in only 11–32% ($P < 0.001$ vs. indexed LV mass). The Framingham Study showed a substantial overlap in septal thickness among subjects with and without echocardiographic LVH defined on the basis of indexed LV mass.[14]

In the present study, the septal thickness criteria tended to classify LVH severity of lesser degree than the indexed LV mass method (i.e. 19.6% of subjects had severe LVH by indexed LV mass compared with only 1.2% by septal thickness). Equally, the agreement between the two methods was much lower in classifying the severity of LVH (kappa = 0.29). Therefore, a large proportion of patients with moderate or severe echocardiographic LVH by indexed LV mass was missed if classified only by septal thickness. In contrast, we found that an increased indexed LV mass was not invariably present in patients with increased wall thickening, consistent with previous reports demonstrating that various stressors may have more influence on LV wall thickness than chamber size.[15,16]

The mechanisms responsible for this considerable interindividual variability in LV mass increase are beyond the scope of this study. It seems likely that the presence of unmeasured risk factors, including genetic risk factors and multiple variants, may be involved in modulating a complex trait such as the development and pattern of LVH.[17] Accordingly, in a large cohort study, multivariable models accounting for known risk factors explained only 50% of the variability of LV mass as assessed by echocardiography.[18]

## Discordance between left ventricular wall thickness and mass

We examined the clinical and echocardiographic characteristics associated to the discrepancy in LVH categorization. One notable result was that those patients in whom LVH was identified by only one echocardiographic criterion in general had no significant difference in risk factors, medical history, or echocardiographic characteristics when compared with the concordant groups with LVH present by both criteria, apart from for the higher prevalence of diabetes. These findings are not surprising considering that cardiac hypertrophy *in vivo* is a multifactorial disease and that the natural history of the challenged heart is a 'continuum' in which the overall thickness or mass modifications of the LV can all take place at various stages of cardiac disease.[19]

Notwithstanding, in our population a history of diabetes was associated to the presence of discordance in the diagnosis of LVH. This finding parallels the result of studies[16,20] showing that, in the clinical context, the presence of metabolic syndrome and diabetes have a distinctive influence on the evolution of the LV remodelling despite an indistinguishable initial cardiac insult.

Previous data reported that diabetes accelerates the development of LVH independent of arterial pressure.[21] In a cross-sectional population-based study, increase in wall thickening without increase in LV mass characterized the main modality by which metabolic syndrome abnormalities influenced cardiac structure. The Authors hypothesized that these findings were consistent with a possible influence of underlying factors such as insulin resistance and a haemodynamic or vascular process on myocardial thickening.[16]

In clinical practice, it is important to distinguish this unique phenotype since the abnormal relative wall thickness/normal mass LV remodelling pattern represents a stronger cardiovascular risk factor in diabetic than non-diabetic patients.[20]

### Reclassification of left ventricular hypertrophy and prognosis

Ideally, to provide normative data about the degree to which echocardiographic LVH measurements deviate from normal, a practical approach that predict outcomes or prognosis would be preferred.[2] However, the use of linear dimensions for LVH determination presents potential limitations. Indeed, M-mode echocardiography does not allow one to identify the distribution of hypertrophy in the ventricular septum precisely. This is the case when those portions of the septum which are thickened are not accessible to the M-mode ultrasonic beam, typically in hypertrophic cardiomyopathy patients where the heterogeneous distribution of hypertrophy results in a distortion of internal LV shape allowing algorithms, generally used to measure LV mass, not applicable in this disease.[22] Limitation notwithstanding, our data demonstrated that both the indexed LV mass and LV thickness partition values proposed by the ASE/EAE were strongly related to death and were able to entail a risk gradient. Notably, the prognostic accuracy for the model including the four degrees of indexed LV mass was superior to the model based on the septal thickness partition values. In addition, at multivariable analyses, after adjusting for age, gender, LV ejection fraction, atrial fibrillation, presence of greater than moderate valvular heart disease, and LV wall motion score index, indexed LV mass partition values retained a significant association with death, whereas LV septal thickness values were no longer significant. Furthermore, when both definitions were considered contemporary, only the indexed LV mass classification of LVH severity maintained a statistical significant and graded association with death.

Our data reinforce previous findings demonstrating that indexed LV mass represented a strong independent marker of cardiovascular risk both in the general population[23–26] and in high-risk groups[27–31] and suggest that, given its prognostic utility, should be preferred to qualify LVH severity.

## Limitations and strengths

The present study population was referral based, and the extent to which the data can be generalized to other populations remains unknown. Particularly, because the vast majority of subjects enrolled was Caucasian results may not be applicable to other ethnicities.

Information on risk factors was retrievable only for 73% of the patients. For this reason multivariable analysis including risk factors as covariates was performed separately as ancillary analysis.

Strengths of the study include the real-time contemporary measurement of LV mass and septal thickness in a large number of unselected outpatients and completeness of follow-up.

## Conclusions

The application of the ASE/EAE recommended formula and cut-offs of indexed LV mass and septal wall thickness produced a significantly different echocardiographic classifications of LVH degree. Furthermore, the categorization based on measurement of indexed LV mass provided greater prognostic information than septal thickness. Therefore, this parameter should be preferred when evaluating subjects for the presence and severity of echocardiographic determined LVH.

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