

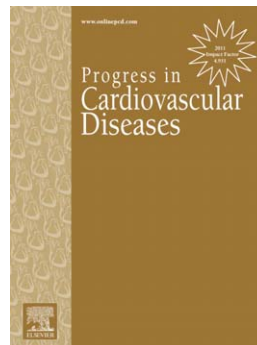
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Invited Manuscript Progress in Cardiovascular Diseases

Impact of Echocardiographic Left Ventricular Geometry on Clinical Prognosis

Carl J. Lavie, M.D.^{1,2}, Dharmendrakumar A. Patel, M.D., MPH³, Richard V. Milani, M.D.¹,
Hector O. Ventura, M.D.¹, Sangeeta Shah, M.D.¹, Yvonne Gilliland, M.D.¹

From the Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute,
Ochsner Clinical School – University of Queensland School of Medicine, New Orleans
Louisiana¹; the Department of Preventive Medicine, Pennington Biomedical Research Center,
Louisiana State University System, Baton Rouge Louisiana²; U T Erlanger Cardiology, Erlanger
Health System, Chattanooga Tennessee³

Address Correspondence to:

Dr. Carl J. Lavie

Department of Cardiovascular Diseases

John Ochsner Heart and Vascular Institute

University of Queensland School of Medicine

1516 Jefferson Hwy.

New Orleans, LA 70123

Phone (504) 842-5874

Fax (504) 842-5875

clavie@ochsner.org

Abbreviations:

AF: Atrial fibrillation

ASE: American Society of Echocardiography

BP: Blood pressure

BSA: Body surface area

CFR: Coronary flow reserve

CHD: Coronary heart disease

CR: Concentric remodeling

CV: Cardiovascular

DD: Diastolic dysfunction

ECG: Electrocardiographic

HF: Heart failure

HTN: Hypertension

LAE: Left atrial enlargement

LAVI: Left atrial volume index

LV: Left ventricular

LVEF: Left ventricular ejection fraction

LVH: Left ventricular hypertrophy

LVM: Left ventricular mass

LVMI: Left ventricular mass index

RWT: Relative wall thickness

SCD: Sudden cardiac death

VEA: Ventricular ectopic activity

Abstract

Abnormal left ventricular (LV) geometry, including LV hypertrophy (LVH), is associated with increased risk of major cardiovascular (CV) events and all-cause mortality and may be an independent predictor of morbid CV events. Patients with LVH have increased risk of congestive heart failure, coronary heart disease, sudden cardiac death and stroke. We review the risk factors for LVH and its consequences, as well as the risk imposed by concentric remodeling (CR). We also examine evidence supporting the benefits of LVH regression, as well as evidence regarding the risk of CR progressing to LVH, as opposed to normalization of CR. We also briefly review the association of abnormal LV geometry with left atrial enlargement and the combined effects of these structural cardiac abnormalities.

Abnormalities in left ventricular (LV) geometry, including LV hypertrophy (LVH), are targeted responses to chronic arterial hypertension (HTN) and other cardiovascular (CV) disorders; and LVH is an independent risk factor for coronary heart disease (CHD), heart failure (HF), arrhythmias, including sudden cardiac death (SCD), stroke, and other major CV morbidity and mortality.¹ According to Laplace's law, in the short-term, increases in LV mass (LVM) may be beneficial by allowing for a reduction in LV wall stress and hemodynamic compromise. On the other hand, in the long-term, LV geometric abnormalities, particularly LVH, can deteriorate to maladaptive processes and increase the risk of HF and other CV disorders.² Clearly, numerous epidemiological studies have demonstrated that LVH is not benign but is associated with very high prevalence of morbid CV events, and in most instances, LVH seems to be a more potent risk factor than other conventional CV risk factors for predicting major CV morbidity and mortality.^{1,3-6}

In this review, we discuss the various types of LV geometric abnormalities, including concentric remodeling (CR) and concentric and eccentric LVH (cLVH and eLVH, respectively). We also review the risk factors for LVH, its consequences, and implications for regression. Additionally, we review the more subtle LV geometric abnormality of CR and its predictive value for CV events, as well as implications for preventing the conversion of CR to frank LVH. Finally, we discuss the impact of obesity on LV geometric abnormalities and the association of LV geometric abnormalities with other structural abnormalities, particularly left atrial enlargement (LAE).

Risk Factors

The major risk factors for LVH are listed in Table 1. Epidemiologic studies have identified age, elevated blood pressure (BP) and weight as independent risk factors for the development of LVH.^{1,7} Obviously, BP and weight typically increase with age, not surprisingly markedly increasing the prevalence of LVH in the elderly. LVH is also related with other conditions including diabetes,⁸ hypercholesterolemia,⁹ myocardial infarction,¹⁰ valvular stenotic and regurgitant lesions,¹¹ as well as African American race.¹² Additionally, high sodium intake, independent of level of BP, also increases the prevalence of LVH,^{1,7} as do other factors listed in Table 1.

Consequences of LVH

As discussed earlier, although initially LVH may be compensatory and benign, for decades it has been known to be associated with numerous adverse CV consequences (Table 2 and Figure 1). More than 3 decades ago, data from the Framingham Heart Study demonstrated that definite electrocardiographic (ECG) evidence of LVH, both by voltage and with repolarization abnormalities or "strain" pattern on the ECG, was associated with 6-fold and 8-fold increases in CHD and CV mortality, respectively.¹⁰ Clearly, as LVH as assessed by LVM index (LVMI) increases, so does the risk of major CV events.

Coronary Flow Reserve (CFR) The ability of the coronary arteries to increase their blood flow under stress is referred to as CFR, which is markedly reduced in patients with LVH due to HTN or aortic stenosis.^{1,13}

LV Function Certainly, LVH is associated with development of HF with either preserved or reduced levels of systolic function.² Clearly, ECG-LVH with "strain" pattern predicts both new onset HF and increased mortality, with LVH predicting HF events more so than CHD events.¹⁰

Although the exact mechanism by which LVH impacts LV function is not totally known, LVH and myocardial fibrosis may adversely affect diastolic dysfunction (DD). Although LVM and relative wall thickness (RWT) may both increase DD in HTN, studies have also demonstrated that combined HTN and obesity (discussed below) have significant adverse impact on LV diastolic filling.^{1,7} Although LVH is associated more strongly with DD than with systolic dysfunction,^{1,7,13} we recently demonstrated that 13% of patients with preserved LV systolic function but with cLVH progressed to LV systolic dysfunction during 3-year follow-up, indicating that LVH impacts diastolic and systolic HF.²

Ventricular Ectopic Activity (VEA) Messerli and colleagues² demonstrated three decades ago that ECG-LVH was associated with the high prevalence of premature and complex VEA, which may partly explain the known association of LVH, especially ECG-LVH, with increased risk of SCD. Several echocardiographic studies have demonstrated increased risk of complex VEA and risk of SCD,^{5,15} whereas regression of LVH may be associated with reduced risk of SCD.¹⁶

Additionally, LVH is a strong risk factor for atrial fibrillation (AF),^{17,18} including a 20% increase in the risk of AF for every one standard deviation increase in LVM.¹⁷ Also, ECG-LVH appears to be an independent risk factor for AF,¹⁸ whereas regression of ECG-LVH was associated with reduced risk of AF.¹⁹

Increased CV Events Early studies from the Framingham Heart Study demonstrate marked increases in CHD events, HF, and SCD associated with ECG-LVH.¹⁰ During the last three decades, two studies from the Framingham Heart Study^{3,20} and elsewhere^{4,6} all clearly demonstrate marked increases in CV morbidity and mortality associated with echocardiographic LVH.^{1,7} Typically, studies have demonstrated a greater increase in CV risk across the spectrum of LVM and LVH.^{1,21} The risk associated with specific LV geometric profiles is discussed below.

In addition to CV diseases, LVH also appears to be associated with and predictive of renal endpoints and other target organ damage.^{1,22} However, despite the very strong association of LVH with CV and non-CV risk, LVH is not often included as a standard CV disease risk factor.

Specific Abnormalities in LV Geometry

Typically, HTN and other CV disorders can include 4 distinct patterns of LV geometry based on the relationship between LV cavity size and RWT, including CR, as well as eLVH and cLVH (Figure 2).²³

The subtle LV geometric abnormality of CR is defined as an increase in RWT with normal LVMI, whereas increased LVMI indicates LVH, either cLVH if RWT is also increased or eLVH if RWT is normal. Although the exact cut-points have varied (e.g. one classification defined $RWT \geq 0.45$ as increased and $LVMI > 125 \text{g/m}^2$ as increased), the American Society of Echocardiography (ASE) currently defines increased LVMI as $> 115 \text{g/m}^2$ for men and > 95

g/m^2 in women and RWT, calculated as $2 \times$ posterior wall thickness in diastole/LV internal diameter > 0.42 .²⁴

Alterations in LV geometry other than LVH have not typically been appreciated as important CV risk factors.^{1,25} However, many studies have demonstrated that specific LV geometry and type of LVH may be an important factor in CV diseases, including HTN (Figure 3).⁴ In fact, Koren et al⁴, in a large study of patients with HTN, demonstrated an over 2-fold increase in CV events in those with CR compared with normal LV geometry, with CV events markedly and progressively increasing with eLVH and cLVH.

Recently, we have assessed the prevalence of abnormal LV geometry in echocardiographic patients with normal left ventricular ejection fraction (LVEF), defined as $\geq 50\%$, demonstrating that over one-third had CR, and over 10% had echocardiographic LVH, almost evenly divided between eLVH and cLVH.²⁵ In a study of 35,602 patients with normal LVEF, Milani et al²⁵ demonstrated marked increases in mortality associated with CR, similar to that noted with eLVH, with a further marked increase in mortality with cLVH (Figure 4). Since patients with reduced LVEF or advanced valvular heart disease were not included in this study, eLVH may not carry as high of a risk compared with some HF or valvular heart disease studies. In a study by Lavie et al²⁶ in patients > 70 years of age, CR was present in 43% of elderly, and in this elderly cohort, CR and cLVH were associated with marked increases in mortality compared with normal LV geometry and even more than those with eLVH.

Impact of Obesity

As previously discussed, obesity is one of the strongest predictors for abnormal LV geometry, including LVH, and typically obesity increases with age and is a strong risk factor for HTN.^{1,7,27} Clearly, we have recently demonstrated that abnormal LV geometry, including both CR and both eLVH and cLVH, are more common in obese than leaner patients, with the same impact of obesity on abnormal LV geometry noted in both women and men.^{27,28}

Additionally, we have identified a strong "obesity paradox" in many cohorts with CV diseases, as discussed in detail elsewhere.²⁹⁻³² Despite the increased prevalence of abnormal LV geometry in obesity, which is typically associated with worse overall CV prognosis, we still demonstrated better survival among obese men and women compared to their leaner counterparts.^{27,28} In fact, for every LV geometric profile (normal LV geometry, CR, eLVH and cLVH), obese had lower mortality than did the leaner patients (Figure 5).²⁸

In our studies, we define LV geometry as recommended by the ASE and as used in many trials, and we indexed LVM to body surface area (BSA), using the LVMI method.²⁴ However, many obesity researchers have suggested correcting LVM for some height or other allometric correction (e.g. height^{2.7}, using a cut-off of 50 g/m^{2.7} to define LVH) that may correlate better with lean body mass and reduce the variability in cohorts of normal subjects.^{1,33} Nevertheless, in our laboratory, correcting LVM for either BSA or height had similar prognostic power in obese and lean patients, and the BSA method predicted mortality slightly better than did the height method.^{27,28}

LV Geometry and Left Atrial Enlargement

It is well known that there is a close relationship between left atrial enlargement (LAE) and DD. Although numerous methods to assess DD by echocardiography are available, including pulsed-Doppler of mitral inflow and mitral annular tissue Doppler imaging,³⁵ which are beyond the context of this manuscript, a common result of many LV structural and functional abnormalities, including DD, is LAE.³⁵⁻³⁷ Likewise, studies indicate that LVH is an independent predictor of LA size.³⁵ In a study of 47,865 patients with LVEF $\geq 50\%$, we determined that both RWT and LVMI were independent predictors of LAE. Although CR was associated with slight, but significant, increase in the prevalence of LAE, both eLVH and cLVH, were associated with two-fold increases in the prevalence of LAE. Furthermore, LAE was independently associated with abnormalities in LV geometry.³⁵ Prior studies have indicated that LAE as assessed by left atrial volume index (LAVI) was a powerful predictor of survival in patients with CV diseases.³⁶ In a similar way, the combination of abnormal LV geometry and LAE in our study was associated with additive effects on increasing all-cause mortality.³⁷ Mild, moderate and severe LAE by LAVI were associated with 10%, 46% and 2.5-fold increased risk of mortality, respectively.³⁷ In patients with normal LV geometry or CR, severe LAE was associated with increased mortality by 28% and 46%, respectively. However, in eLVH and cLVH, the mortality risk with severe LAE was twice that of patients with a normal LAVI.³⁷

Regression of Abnormal LV Geometry

It is well known from both animal and human studies that anti-HTN therapies may cause regression of LVH and could be associated with reductions in CV morbidity and mortality.^{1,38-44} Additionally, reversing LVH has been shown to improve systolic and diastolic function, improve abnormal CFR, and reduce overall CV risks.^{1,3,40,41}

Another noteworthy finding from our data was that subjects with CR who reverted to a normal LV geometric pattern over time had improved survival, whereas those who converted from CR to LVH had marked increases in mortality (Figure 6).²⁵ These data suggest that changes in CR over time may impact prognosis, similar to the many studies suggesting improvements in prognosis with regression of LVH.^{1,25} Therefore, improvements in LV geometry, including both CR and LVH, may be associated with overall benefits on CV prognosis and all-cause survival.

Conclusions

The constellation of findings suggests that abnormalities in LV geometry, including LVH, and, particularly, the more subtle finding of CR, are extremely common in patients referred for echocardiography, even those with preserved LVEF. These abnormalities in LV geometry frequently coexist with other structural abnormalities, including LAE; and both abnormal LV geometry and LAE are associated with significant increases in mortality risk. We believe that routine echocardiographic reports should include data on LV geometry, including CR as well as LVH (both eLVH and cLVH). Studies are needed to determine strategies to reduce abnormalities in LV geometry, which may be associated with improved prognosis in CV diseases.

Table 1. Risk Factors for LVH

Major
<ul style="list-style-type: none">• Age• Arterial pressure (including ambulatory, work, and exercise)• Weight
Other
<ul style="list-style-type: none">• Race (Higher in African Americans)• Renin-angiotensin-aldosterone system• Increased sodium intake• Diabetes• Aortic stenosis and regurgitant valvular heart disease• Catecholamines• Job strain, including physical and emotional• Various growth factors

Table 2. Consequences of LVH

- Reduced coronary flow reserve
- Reduced ventricular functional systolic reserve
- Diastolic ventricular dysfunction
- Increased coronary artery disease
- Frequent and complex ventricular arrhythmias
- Increased cardiovascular events
- Increased cardiovascular mortality

Figure Legends

1. Risk factors and consequences of LVH.
2. Hemodynamic and geometric profiles in hypertensive patients with the 4 patterns of LV geometry. The short axis/long axis ratio (b/a) was described by 2-dimensional echocardiography. CI, cardiac index (l/min/m²); SBP, systolic blood pressure; TPR, total peripheral resistance (dynes s cm⁻⁵). Reproduced with permission from Ganau A et al.²³
3. Relation of LV geometry to mortality in patients with uncomplicated hypertension. CH, concentric hypertrophy; EH, eccentric hypertrophy; NL, normal. Relative wall thickness is the ratio of the posterior wall thickness to one-half the left ventricular internal dimension at end-diastole. Reproduced with permission from Koren MJ et al.⁴
4. Actuarial cumulative hazard plot for survival time based on cardiac structure. A, Normal structure, CR, and frank LVH. B, Normal structure, CR, eccentric hypertrophy (EH), and concentric hypertrophy (CH). Reproduced with permission from Milani RV et al.²⁵
5. Patients with CR who progress to LVH versus subjects who convert to normal (NL) cardiac structure. A, Kaplan-Meier survival over 3 years. B, RRs and 95% CIs of all-cause mortality. Reproduced with permission from Milani RV et al.²⁵
6. Mortality prevalence in four LV geometric patterns by obesity status in female patients with normal ejection fraction. Reproduced with permission from Patel DA et al.²⁸

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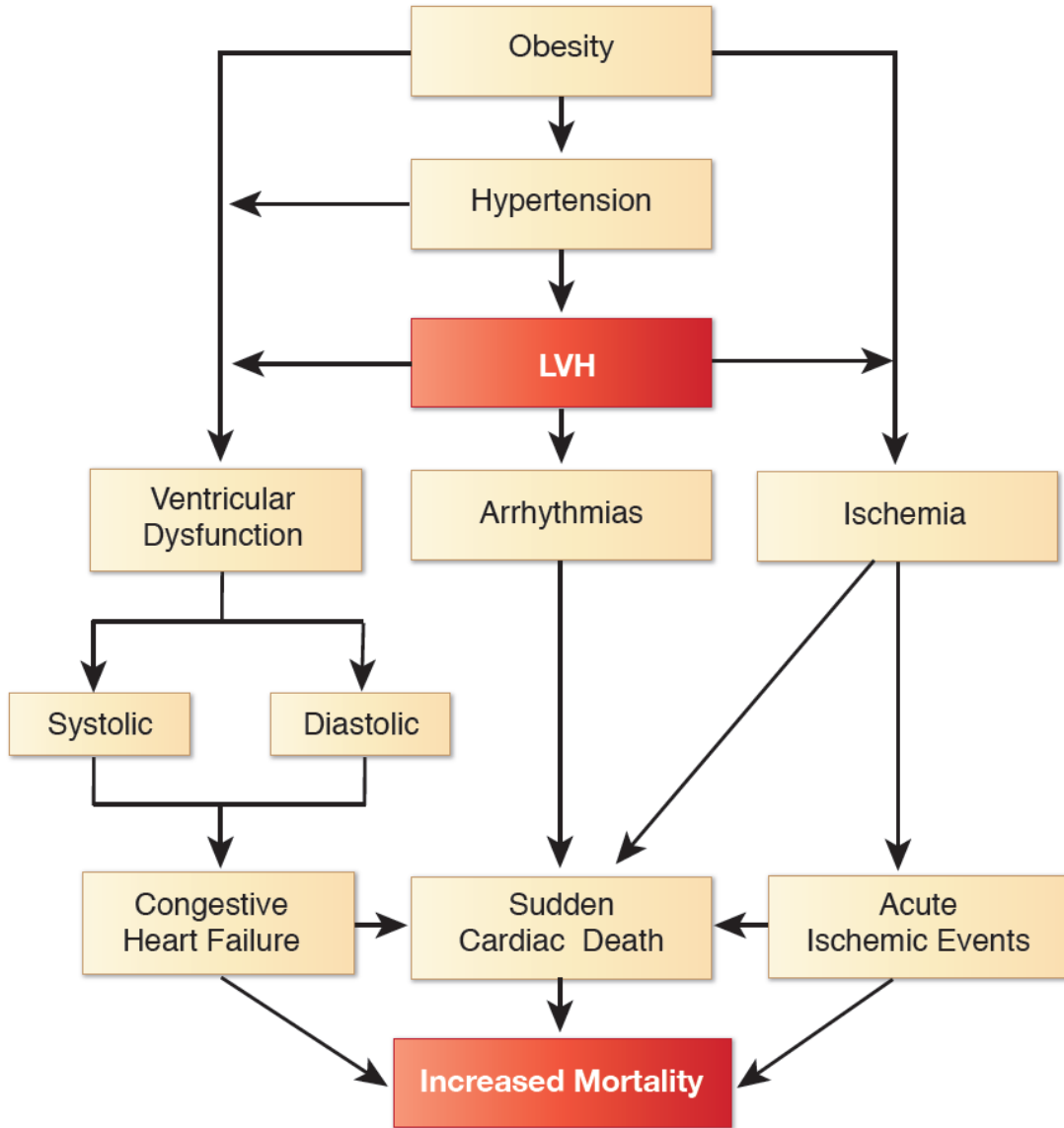


Fig 1

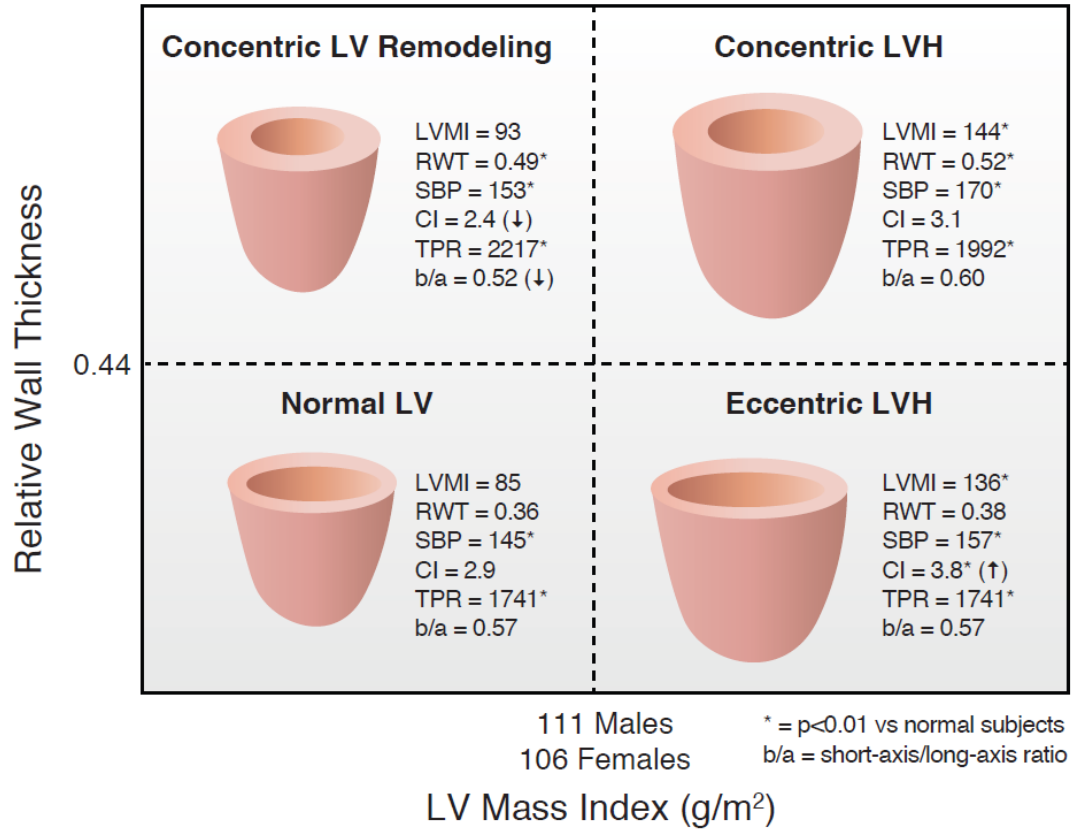


Fig 2

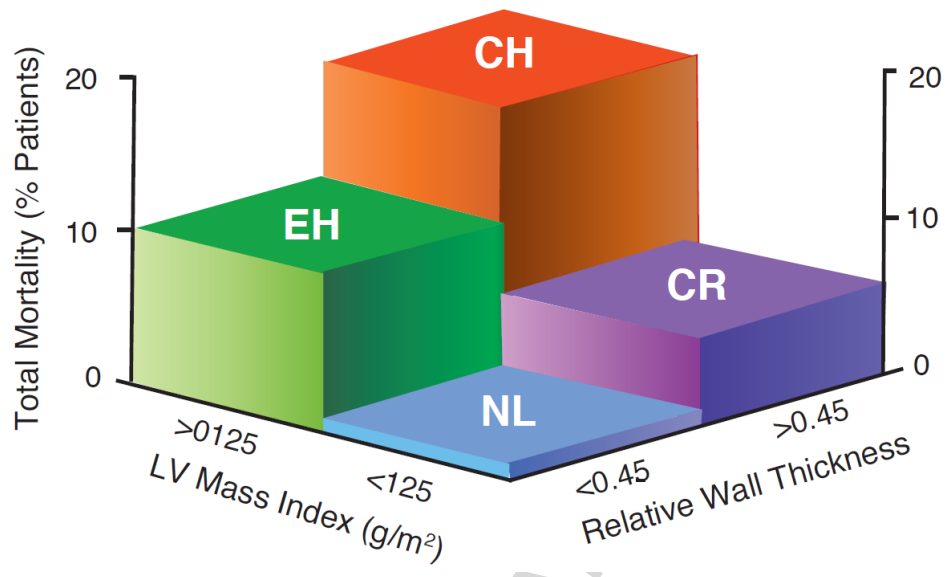


Fig 3

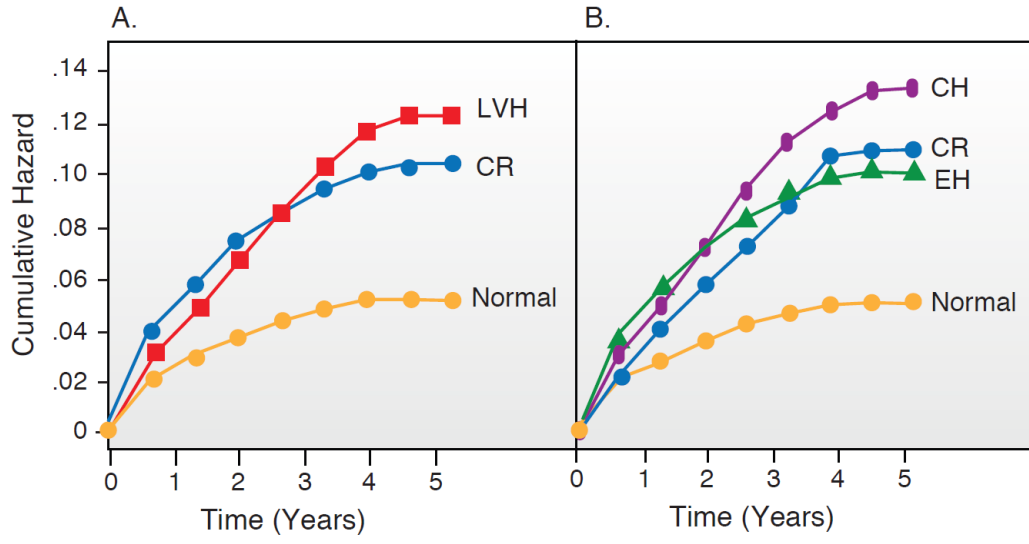


Fig 4

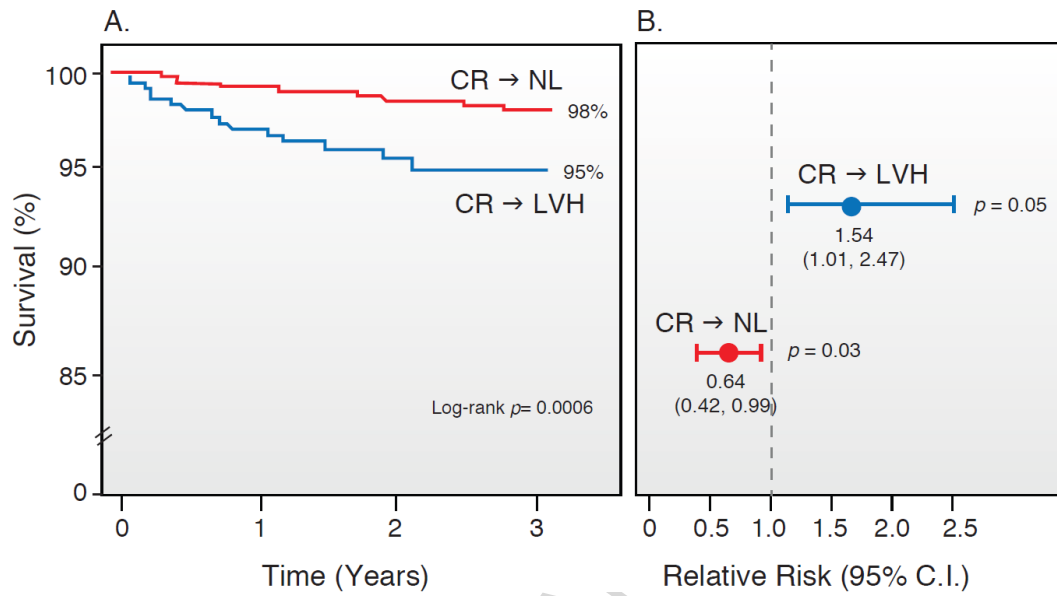


Fig 5

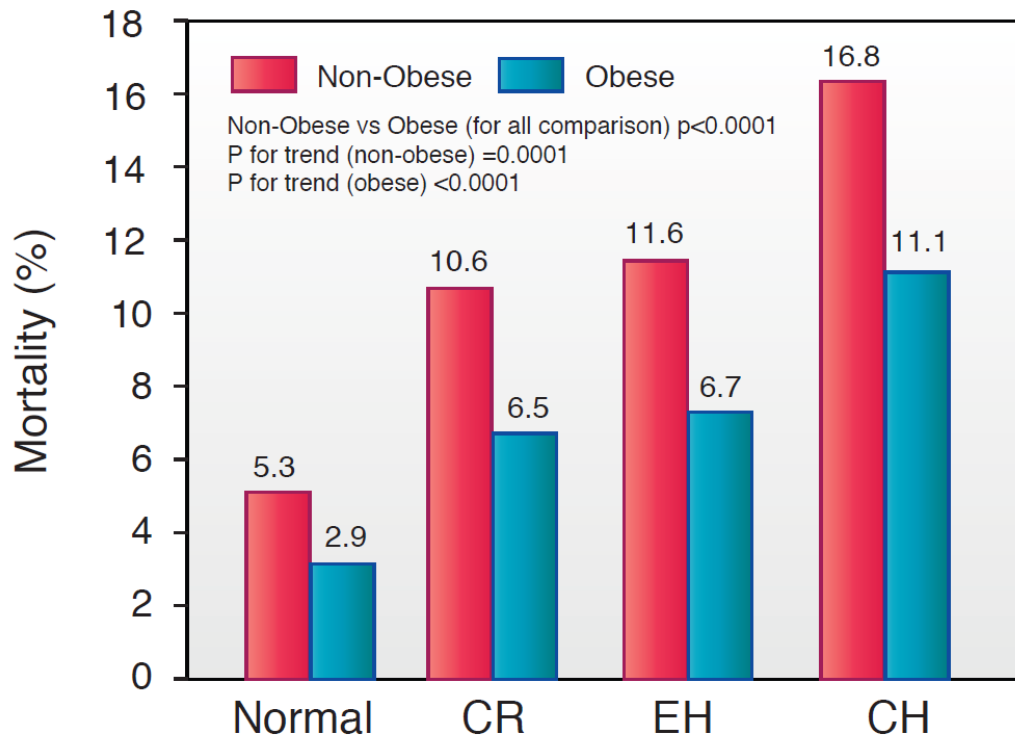


Fig 6