OA Evidence-Based Medicine
Open Access

Review

Systematic Reviews

Regression of left ventricular hypertrophy: lessons from clinical trials

P Pokharel[1], JN Bella[1,2]*

Abstract

Introduction

Hypertension is an epidemic that affects more than 1 billion people worldwide annually. Left ventricular hypertrophy is the phenotypic expression of hypertensive heart disease, which depends on complex interactions among genetic makeup, environmental factors and lifestyle. Left ventricular hypertrophy has been shown to be independently associated with adverse cardiovascular morbidity and mortality. Targeting left ventricular hypertrophy with different pharmacological agents and lifestyle modifications has been associated with favourable results and results in improved outcome. Evidence shows that the drug targets rennin–angiotensin–aldosterone are more effective system in reducing left ventricular mass. Moving forward, the new frontier in this field will be to understand the genetic influences on left ventricular hypertrophy regression and progression and ways to intervene early and treat this public health burden.

Conclusion

Targeting left ventricular hypertrophy regression with various antihypertensive agents results in improved clinical outcomes. Therefore regression of LVH can be considered surrogate endpoint in the treatment of hypertensive heart disease

* Corresponding author
Email: jonnbella@earthlink.net

[1] Department of Medicine, Division of Cardiology, Bronx-Lebanon Hospital Center, New York, NY 10457, USA
[2] Albert Einstein College of Medicine, Bronx, NY 10461, USA

Introduction

Hypertension affects approximately 1 billion of population worldwide and approximately 50 million in USA annually. Increase in blood pressure (BP) has been shown consistently to increase the risk of cardiovascular morbidity and mortality through end-organ dysfunction. This risk appears to be linear and independent of other cardiovascular risk factors.

Left ventricular hypertrophy (LVH) is the phenotypic expression of hypertensive heart disease. In response to increased afterload in hypertensive patients, LV mass increases as an adaptive process to reduce LV wall stress. However, if the increase in the afterload persists, the adaptive response turns maladaptive. The data from Framingham cohort and work by other investigators demonstrate that this increase in LV mass independently predicts cardiovascular morbidity and mortality[1–3]. There is good evidence supporting pharmacological therapies and lifestyle modifications targeting BP, during which LVH translates into improved clinical outcome. This paper discusses outcomes of clinical trials on regression of LVH.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Prognostic implication of left ventricular hypertrophy

There is robust data indicating association between LVH and increased cardiovascular morbidity and mortality (Table 1). Levy et al.[1] reported that LVH, quantified by echocardiography, independently predicts cardiovascular morbidity and mortality. A total of 3320 participants, aged more than 40 years and free of cardiovascular disease, were enrolled in the Framingham Heart Study for 4 years[1]. There were total 208 cardiovascular events, 37 cardiovascular deaths and 124 all-cause deaths. The relative risk (RR) for developing cardiovascular disease was 1.49 in men and 1.57 in women for every 50 g/m^2 increase in the LV mass above normal. This increment was also associated with higher all-cause mortality (RR = 1.49 and 2.01 in men and women, respectively) and cardiovascular mortality (RR = 1.73 and 2.12 in men and women, respectively). Data from the same cohort also showed that LVH increased the risk of sudden cardiac death, more so in men than women[4].

Hypertensive black adults tend to have higher LV mass odds ratio (OR) = 1.80; 95% CI: 1.29 – 2.51 and OR = 2.50; 95% CI: 1.58 – 3.96, LVH indexed to height and body surface area BSA, respectively) and relative wall thickness when compared with their Caucasian counterparts[5]. In the black population, LVH portends greater cardiovascular risk as compared with other ethnic groups[6] and women fare worse as compared with

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

FOR CITATION PURPOSES: *Pokharel P, Bella JN.* Regression of left ventricular hypertrophy: lessons from clinical trials. OA Evidence-Based Medicine 2013 Nov 30;1(2):13.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Evidence-Based Medicine
Open Access

Review

Table 1 Prognostic implications of LVH: Data from selected studies

Author	Numbers	Design	Endpoints	Results
Levy et al.[1]	3220	Observational >40-years-old subjects from Framingham Heart study with LVH followed up for 4 years	Incidence of CV morbidity, mortallity and all-cause mortality	Increased CV morbidity, mortality and all-cause mortality in both men and women
Haider et al.[2]	3661	Observational. >40-years-old subjects from Framingham Heart Study with LVH followed up for 14 years	Incidence of sudden cardiac death	LVH Independently associated with sudden cardiac death. (HR 1.45 for each 50 g/m in-crease in LV mass)
Haider et al.[3]	7495	Observational. Subjects from NHANES III data set with EKG and other clinical data for at least 10 years	Incidence of cardiovascular motality among whites, Black and Latino with LVH	LVH independently associated with worse CV mortality in all three ethnicities This association was significantly greater in Blacks
Liao et al.[4]	463	Observational Black subjects from hospital registry free of angiographic CAD and good echocardiographic images.	Incidence of CV mortality among Black men and women	Female sex independently associated with worse outcome as compared with male
Liao et al.[5]	1089	Observational Blacks subjects from hospital registry with coronary an-giography and M mode echocardiography followed for 5 years	Effect of LVH on survival as compared with multivessel CAD and reduced systolic function	LVH carries worse prognosis than multivessel CAD or reduced EF (attributable risk 2.4 vs. 2 vs. 1.6, respectively)
Verdecchia et al.[6]	2363	Observational Hypertensive subjects free of CAD followed for mean of 5 years	Incidence of CVA	LVH Indipendently associated with cerebrovascular accident
Vakiili et al.[7]	48545	Meta-analysis of 20 studies	Association between LVH and cardiovascular mor-bidity and all-cause mortality	LVH associated with increased CV morbidity and all-cause mortality across all groups except ESRD.

NHAHES-National Health and Nutritional Examination Studies; LVH, left ventricular hypertrophy; ECG-electrocardiogram; BP-blood pressure: CHF, ; DM.

men in terms of overall mortality and cardiac death[7]. Furthermore, LVH carries more risk than multivessel coronary artery disease (CAD) in this group. Liao et al.[8] showed that among 1089 African Americans who had undergone cardiac catheterisation and M-mode echocardiography, the attributable RR for all-cause mortality was 2.4 with LVH, 2.0 with reduced EF and 1.6 with multivessel CAD. The increase in morbidity and mortality in this group could be partly due to concentric LVH phenotype, which has been independently associated with worse outcomes[2].

Verdecchia et al.[3] showed that for each 29 g/m^2 increase in LV mass, there is a significant independent increase in the risk of stroke (RR = 1.31; 95% CI: 1.09 – 1.58) in hypertensive patients. In a meta-analysis of 20 studies with 48,545 patients, Vakili et al.[9] found that LVH consistently predicted worse cardiovascular morbidity and all-cause mortality across all groups and population except end stage renal disease (ESRD) patients. Mean adjusted risk rates for cardiovascular morbidity and all-cause mortality were 2.3 and 2.5, respectively.

Critical appraisal of the validity of relevant articles

Left ventricular hypertrophy regression

Current evidence suggests that LVH can be targeted through reducing BP by pharmacotherapy and lifestyle

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

FOR CITATION PURPOSES: *Pokharel P, Bella JN.* Regression of left ventricular hypertrophy: lessons from clinical trials. OA Evidence-Based Medicine 2013 Nov 30;1(2):13.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Evidence-Based Medicine
Open Access

modifications. However, agents that lower BP do not necessarily have equivalent effects on LV mass, which suggests that additional factors modulate expression of LVH. It is increasingly being recognised that neurohormonal and genetic factors play an equally important role in the pathogenesis of LVH. Modulating this factor to target LVH is a promising avenue in the future.

All antihypertensive drugs appear to have some effect on LVH regression (Figure 1). While there is no consensus on the best pharmacologic agent to regress LVH, the current evidence favours the drug-targeting renin–angiotensin–aldosterone system (RAAS). Data from bench research showed that activation of the RAAS system causes hypertrophy of cardiomyocyte, much akin to load-induced hypertrophy and fibrosis, both of which are mediated by angiotensin II via angiotension-1 (AT-1) receptor[10]. It has been shown that manipulation of the RAAS system translates to LV regression and outcomes are improved clinically. angiotensin receptor blocker (ARB) seems to have additional class action on LVH regression, independent of BP control, as shown in numerous clinical trials.

The Losartan Intervention for Endpoint Reduction in a Hypertension (LIFE) study showed that losartan-based antihypertensive regimen resulted in a greater reduction in LV mass index from baseline as compared with atenolol-based regimen across all strata (−21.7 ± 21.8 vs. −17.7 ± 19.6 g/m^2, $P = 0.021$)[11]. This reduction was independent of the baseline LV mass index and BP. There was a change in LV geometry and reduced concentricity in both the arms and lesser increment in LV internal diameter with losartan-based treatment. Similar reduction in LV mass was documented using three-dimensional echocardiography and magnetic resonance imaging (MRI) among the hypertensive patients treated with telmisartan as compared with carvedilol[12]. In a Heart Outcome Prevention (HOPE) Study, patients at high risk for CAD were randomly assigned to receive ramipril and placebo, and followed up prospectively for 4.5 years. The study patients treated with ramipril were protected against LVH and regression of LVH was independent of BP with ramipril treatment[13]. The Left ventricular hypertrophy study, Indapamide Versus Enalapril (LIVE study) was a prospective, double-blind study that compared indapamide SR 1.5 mg and enalapril 20 mg in reducing LV mass index in hypertensive patients with LVH[14]. At the end of 48 weeks, indapamide significantly reduced the LV mass index from the baseline (−8.4 ± 30.5 g/m^2 from baseline; $P < 0.001$); whereas enalapril did not (−1.9 ± 28.3 g/m^2) despite the fact that both the drugs significantly reduced BP. Also, the change in LV mass index did not correlate with BP and indapamide progressively reduced the wall thickness throughout the study period. Similarly, the Prospective Randomised Enalapril Study Evaluating Reversal of Ventricular Enlargement (PRESERVE) study evaluated if antihypertensive treatment with enalapril induces greater LVH regression than nifedipine by > 10 g/m^2 despite equivalent BP reduction[15]. A total of 303 patients were followed up for 1 year and there was no difference between the groups in terms of LVH regression from the baseline.

It is not clear whether dual blockage of RAAS with different pharmacological agents will incur incremental benefit in BP control and LV mass reduction. The 4E-Left Ventricular Study was a double-blind study, which studied LVH regression among groups treated with eplerenone, enalapril and eplerenone/enalapril[16]. At the end of 9 months, changes in LV mass were assessed by MRI. The decrease in LVH mass from baseline was statistically significant in all three groups. The eplerenone/enalapril arm was most effective in terms of absolute reduction in LV mass. There was poor correlation between antihypertensive effect of the drug and reduction in the LV mass. However, the data from other studies suggest that there was no additional benefit with dual RAAS blockage. The combination of ramipril and telmisartan had a similar effect on LVH than ramipril alone among the patients at high vascular risk[17]. A similar result was reported from Aliskiren in a Left Ventricular Hypertrophy (ALLAY) trial[18]. A total of 465 patients with hypertension, increased ventricular wall thickness and body mass index > 25 kg/m^2 were randomised to receive aliskiren 300 mg, losartan 100 mg, or their combination daily for 9 months. Cardiac MRI was used to assess LV mass at the baseline and at completion of study. In all the three arms, LV mass regressed significantly from the baseline (−4.9, −4.8, and −5.8 g/m^2 reductions in the aliskiren, losartan, and combination arms, respectively; $P < 0.0001$ for all three arms). However, there was not much difference between monotherapy and combination therapy independent of BP.

The Treatment of Mild Hypertension Study (TOMHS) compared the effects of both pharmacological and non-pharmacological approaches with the treatment of hypertension on LVH regression. It was a double-blind, placebo-controlled trial involving 844 patients with mild hypertension[19]. The patients were advised weight loss and dietary salt reduction, nutritional-hygienic intervention (NH), or NH intervention and randomised to one of the five classes of antihypertensives: (1) chlorthalidone (a diuretic); (2) acebutolol (a β-blocker); (3) doxazosin (an α-antagonist); (4) amlodipine (a calcium channel antagonist); or (5) enalapril (an angiotensin-converting enzyme inhibitor). After a follow-up of 4 years, NH intervention was as effective as NH intervention and pharmacological intervention in reducing LV mass. Interestingly, there was a smaller decrease in BP in the

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

For citation purposes: *Pokharel P, Bella JN.* Regression of left ventricular hypertrophy: lessons from clinical trials. OA Evidence-Based Medicine 2013 Nov 30;1(2):13.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Evidence-Based Medicine
Open Access

NH intervention only arm (9 vs. 13.3 mmHg). All the groups showed a significant decrease in LV mass from baseline and addition of chlorthalidone had modest additional effect on reducing LV mass. Recent analysis of data from the Multiple Risk Factor Intervention Trial (MRFIT) showed that the chlorthalidone-treated cohort had greater LVH regression than the hydrochlorothiazide-treated and usual care groups[20]. This effect was thought to be secondary to greater reduction in BP with chlorthalidone.

In a meta-analysis, Klingbeil et al.[21] identified 80 trials with 146 treatment arms (3767 patients) and 17 placebo arms, and the data were adjusted for treatment duration and diastolic BP. They found a significant difference among different medication classes ($P = 0.004$). Overall, LV mass index was decreased by 13% with angiotensin II receptor antagonists (95% CI: 8 – 18), by 11% with calcium channel antagonists (95% CI: 9 – 13), by 10% with ACE inhibitors (95% CI: 8 – 12), by 8% with diuretics (95% CI: 5 – 10), and by 6% with β-blockers (95% CI: 3 – 8) (Figure 1).

Recently, the focus has been shifted to downstream pathways and oxidative stress in the pathogenesis of LVH. Previous studies have shown that allopurinol reduces oxidative stress. In a recent randomised, double-blind, placebo-controlled study, allopurinol 600 mg/day was shown to reduce absolute LV mass (–2.65 ± 5.91 vs. + 1.21 ± 5.10 g in the placebo group, $P = 0.012$) and LV mass indexed to body surface area (–1.32 ± 2.84 g/m^2 vs. +0.65 ± 3.07 g/m^2 in the placebo group, $P = 0.017$) in patients with type II diabetes mellitus[22]. Non-pharmacological intervention and lifestyle changes aimed at LVH regression involve weight loss, aerobic exercise and low-salt diet[23,24].

Left ventricular hypertrophy regression and outcome

LVH is an adaptive response by the human heart targeted to maintain cardiac output in the face of increased pressure and or volume overload. This compensatory response ultimately regresses into a maladaptive one causing heart failure. This transition is basically determined by the complex interplay of environmental, neurohormonal and genetic factors. Over the last two decades, our understating of the pathophysiology of LVH has greatly improved. As a result, attempts to stem or reverse this phenotypic response using pharmacological agents and lifestyle modifications have been fruitful and new novel approaches are being explored.

Regression of LVH is independently associated with improved cardiovascular outcome (Table 2). Levy et al.[25]. reported reduction in LVH using Cornell voltage criteria was associated with improved cardiovascular outcome in men and women (OR = 0.46, 95% CI: 0.26 – 0.84 and OR = 0.56, 95% CI: 0.30 – 1.04, respectively) after adjusting for age and baseline voltage; whereas worsening or no serial change conferred worse outcome In the same study, the severity of LVH at baseline predicted the outcome in graded manner with the lower quartile associated with lower risk than the highest quartile. In the LVH regression sub-study of the HOPE Trial[13], LVH prevention/regression significantly reduced primary outcome of cardiovascular death, myocardial infarction and death (12.3% vs. 15.4%, $P < 0.006$) and congestive heart failure (9.3% vs. 15.4%, $P < 0.0001$) when compared with LVH persistence/progression. In both the studies LVH was defined by EKG criteria which is less sensitive to echocardiography in defining LVH. Regardless, this association holds even when echocardiography is used to define LV mass.

Verdecchia et al.[26] followed 430 patients with serial echocardiography and 24-hour ambulatory BP monitoring from the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) registry. Total duration of follow-up was 1217 patients/year. They showed a reduction in LV mass

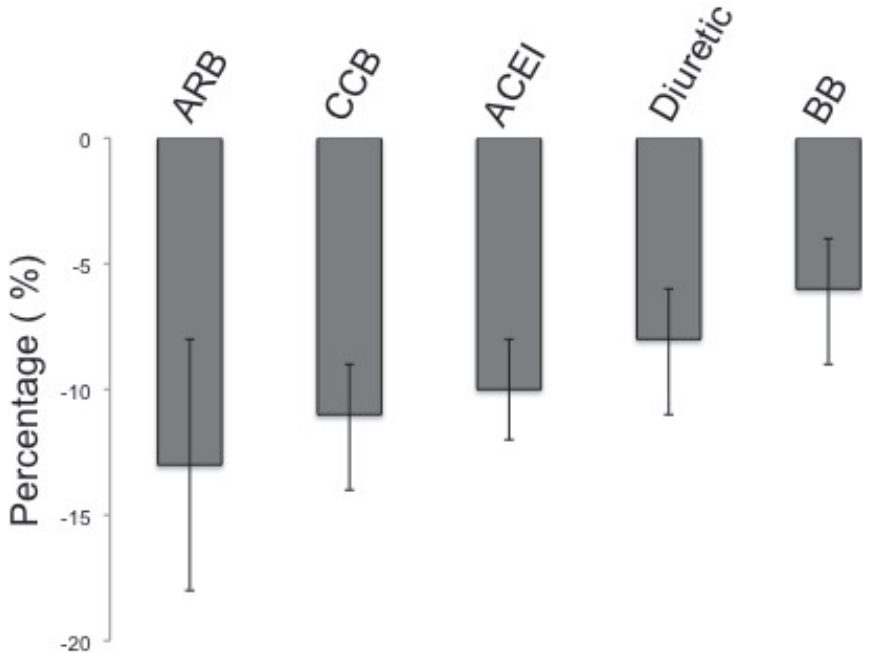

Figure 1: LVH regression with antihypertensive treatment. LVH, left ventricular hypertrophy; ARB angiotensin-receptor blocker,; CCB calcium channel blocker,; ACEI angiotensin converting enzyme inhibitor,; BB beta-blocker, .

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

FOR CITATION PURPOSES: *Pokharel P, Bella JN.* Regression of left ventricular hypertrophy: lessons from clinical trials. OA Evidence-Based Medicine 2013 Nov 30;1(2):13.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Evidence-Based Medicine
Open Access

among the patients with essential hypertension, predicts lower cardiovascular risk [hazard ratio (HR)=0.46, 95% CI: 0.22–0.99, $P < 0.04$) adjusted for baseline LVH. In the same study, the event rate was lower among the subset of patients with LV mass > 125 g/m^2 with LVH regression than the patients whose LV mass remained persistently elevated (1.58 vs. 6.27 events per 100 person-years; $P = 0.002$). In a meta-analysis, the same group showed association between LVH regression and lower cardiovascular decreased events[27]. A total of 1064 hypertensive patients from four studies were included in the analysis and showed that LVH regression reduced the risk of subsequent cardiovascular disease (OR=0.41, 95% CI: 0.21–0.78, $P = 0.007$) as compared with lack of

Table 2 LVH regression and outcome: Data from selected studies

Author	Numbers	Design	Endpoints	Result
Levy. et al.[25]	524	Observational. Subjects from Framingham Heart Study with LVH by ERK were followed. Total of 2660 person examination	Insidence of CV disease	Improvement in EKG features of LVH result in decrease CV risk
Mathew et al.[13]	8281	Randomised, double-blinded case control study comparing ramipril and placebo among high-risk patient Followed for 4.5 years	Prevention, progression and regression of LVH CV death, MI and all-cause death in prevention/ regression arm vs. persistence/progression arm	Patient treated with ramipril protected against LVH Reduction of CHF and composite outcome of CV death, MI and all-cause death in prevention/regression arm
Verdecchis et al.[26]	430	Observational Patient who attended base-line visit and follow-up visit in the setting of PUIMA registry Total 1217 patient year of follow-up	Incidence of CV disease	Regression of LV mass associated with lesser of cardiovascular risk adjusted for baseline LVH
Verdecchia et al.[27]	1064	Meta-analysis. Four studies with LVH defined by echocardiography	LVH regression and CV risk	LVH regression reduced the risk of CV disease
Devereux et al.[28]	941	Prospective, randomised case control study 50–85 years of patient and electrocardiographically determined LVH randomised to losartan and placebo Followed up for 4.8 years	Composite endpoint of CV death, fatal or non-fatal MI and fatal or nonfatal stroke	LVH regression with treatment lowers primary endpoint independent of BP reduction & assigned treatment
Okin et al.[29]	7998	Prospective Randomised, double blind study Hypertensive patient with EKG defined LVH assigned to losartan or Atenolol	New onset DM per 1985 WHO criteria	Regressoin or LV mass progression associated with lower incidence of DM
Wachatell et al.[30]	679	Observational study among participant of LIFF study. Followe up for 3 years	Evaluation LV systolic performance	Regression of LVH with antihypertensive associated with improved strees corrected mid-wall shortening, a marker of systolic performance

PUIMA: Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (Italian Cardiovascular study) ; LVH, left ventricular hypertrophy; ECG-elcetrocardiogram, ; BP-blood pressure, : CHF-congestive heart failure, ; MI-myocardial infarctiom, ;DM-diabetes mellitus.

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

FOR CITATION PURPOSES: *Pokharel P, Bella JN.* Regression of left ventricular hypertrophy: lessons from clinical trials. OA Evidence-Based Medicine 2013 Nov 30;1(2):13.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Evidence-Based Medicine
Open Access

regression or development of new LVH.

In the LIFE Echo Study, 941 patients aged between 55 and 80 years with essential hypertension and electrocardiographic and echocardiographic evidence were followed for a mean of 4.8 for composite endpoint of cardiovascular death, fatal and nonfatal myocardial infarction and fatal or nonfatal stroke[28]. The composite endpoint occurred in 11% of the patients and Cox regression analysis showed a strong association between LVH regression with treatment and composite endpoint [HR = 0.78 per 1-SD (25.3) decrease in LV mass index; 95% CI: 0.65 – 0.94; $P = 0.009$] independent of reduction in the BP and assigned treatment. There was a parallel independent association between LVH regression and lower cardiovascular mortality, all-cause mortality and myocardial infarction.

Interestingly, regression or absence of progression of LV mass has been reported to be associated with lower incidence of diabetes mellitus[29]. In addition, LVH regression has been reported to improve LV systolic performance[30]. A total of 679 hypertensive patients with electrocardiogram (ECG) evidence of LVH from the LIFE sub-study were followed with a yearly echocardiogram during 3 years of antihypertensive treatment. During this period, the mean BP reduction and LV mass regression were approximately 15% and 17%, respectively, and the stress-corrected mid-wall fractional shortening increased from 97 ± 13 to 105 ± 12% ($P < 0.001$). This improvement was independently inversely related to changes in LVM ($\beta = -0.211$) and relative wall thickness (RWT) ($\beta = -0.334$). Thus, LVH regression also improved LV systolic function.

Conclusion

LVH is a result of complex interaction among genetic makeup, lifestyle and environment factors. It represents the end organ dysfunction in HTN and other disease. Multiple studies have shown that LVH is an independent risk factor of increased cardiovascular morbidity and mortality and is of major public health burden. Evidence suggests that targeting LVH regression is possible and results in improved clinical outcomes. Therefore regression of LVH can be considered surrogate endpoint in the treatment of hypertensive heart disease. Among various drugs, the ones targeting RAAS, in particular ARBs, appear to have class actions in reducing LV mass independent of BP control. More recently, allopurinol, which reduces oxidative stress at tissue level, may reduce LV mass in type II diabetes mellitus. It remains unclear if this reduction in LV mass translates into improved outcome.

In the last two decades, there have been dramatic advances in personalised medicine and personalised risk prediction. However, attempts to understand and predict the risk associated with LVH through genomics have been a mixed bag of success[31]. This is because the complex phenotype of LVH is not in its entirety and stems from our genetic constitution rather than its interaction between environment and our lifestyle. Moving forward, the new frontier in this field will be to understand the genetic architecture through new study design and genomic technologies and identify its impact on progression and/or regression of LVH.

Clinical applicability

LVH is phenotypic expression of end organ dysfunction associated with increased stroke work modulated by complex interplay of genetic make of an individual, life style and environment. As discussed above it is independently associated with increased cardiovascular morbidity and mortality. LVH regression through pharmacological intervention and life style modification has positive prognostic impact on cardiovascular morbidity and mortality independent of blood pressure reduction. Therefore, it can be used a surrogate marker assessing the treatment effect of antihypertensive treatment on prognosis. Tailoring of antihypertensive regimen to consist of various pharmacological agents that mechanistically act on different levels may be more effective in regressing LV mass and could translate into better clinical outcomes.

Abbreviations list

ALLAY, Aliskiren in a Left Ventricular Hypertrophy study; BP, blood pressure; CAD, coronary artery disease; HOPE, Heart Outcome Prevention study; HR, hazard ratio; LIFE, Losartan Intervention for Endpoint Reduction in a Hypertension study; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; MRFIT, Multiple Risk Factor Intervention Trial; NH, nutritional-hygienic; PIUMA, Progetto Ipertensione Umbria Monitoraggio Ambulatoriale; PRESERVE, Prospective Randomised Enalapril Study Evaluating Reversal of Ventricular Enlargement study; RAAS, renin-angiotensin-aldosterone system; RR, relative risk; TOMHS, Treatment of Mild Hypertension Study.

References

1. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990 May;322(22):1561–6.
2. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med. 1991 Mar;114(5):345–52.
3. Verdecchia P, Porcellati C, Reboldi G, Gattobigio R, Borgioni C, Pearson TA, et al. Left ventricular hypertrophy as an independent predictor of acute cerebrovascular events in essential hypertension. Circulation. 2001 Oct;104(17):2039–44.

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

FOR CITATION PURPOSES: *Pokharel P, Bella JN.* Regression of left ventricular hypertrophy: lessons from clinical trials. OA Evidence-Based Medicine 2013 Nov 30;1(2):13.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Evidence-Based Medicine
Open Access

Review

4. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. J Am Coll Cardiol. 1998 Nov;32(5):1454–9.
5. Kizer JR, Arnett DK, Bella JN, Paranicas M, Rao DC, Province MA, et al. Differences in left ventricular structure between Black and White hypertensive adults: the Hypertension Genetic Epidemiology Network Study. Hypertension. 2004 Jun; 43(6):1182–8.
6. Havranek EP, Froshaug DB, Emserman CD, Hanratty R, Krantz MJ, Masoudi FA, et al. Left ventricular hypertrophy and cardiovascular mortality by race and ethnicity. Am J Med. 2008 Oct;121(10): 870–5.
7. Liao Y, Cooper RS, Mensah GA, McGee DL. Left ventricular hypertrophy has a greater impact on survival in women than in men. Circulation. 1995 Aug;92(4): 805–10.
8. Liao Y, Cooper RS, McGee DL, Mensah GA, Ghali JK. The relative effects of left ventricular hypertrophy, coronary artery disease, and ventricular dysfunction on survival among black adults. JAMA. 1995 May;273(20):1592–7.
9. Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. Am Heart J. 2001 Mar;141(3): 334–41.
10. Sadoshima J, Izumo S. Molecular characterization of angiotensin II-induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the AT1 receptor subtype. Circ Res. 1993 Sep;73(3):413–23.
11. Devereux RB, Dahlof B, Gerdts E, Boman K, Nieminen MS, Papademetriou V, et al. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. Circulation. 2004 Sep;110(11):1456–62.
12. Galzerano D, Tammaro P, Viscovo L, Lama D, Galzerano A, Breglio R, et al. Three-dimensional echocardiographic and magnetic resonance assessment of the effect of telmisartan compared with carvedilol on left ventricular mass: a multicenter, randomized, longitudinal study. Am J Hypertens. 2005 Dec;18(12 Pt 1):1563–9.
13. Mathew J, Sleight P, Lonn E, Johnstone D, Pogue J, Yi Q, et al. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. Circulation. 2001 Oct;104(14):1615–21.
14. Gosse P, Sheridan DJ, Zannad F, Dubourg O, Gueret P, Karpov Y, et al. Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: the LIVE study. J Hypertens. 2000 Oct;18(10):1465–75.
15. Devereux RB, Palmieri V, Sharpe N, De Quattro V, Bella JN, de Simone G, et al. Effects of once-daily angiotensin-converting enzyme inhibition and calcium channel blockade-based antihypertensive treatment regimens on left ventricular hypertrophy and diastolic filling in hypertension: the prospective randomized enalapril study evaluating regression of ventricular enlargement (PRESERVE) trial. Circulation. 2001 Sep;104(11):1248–54.
16. Pitt B, Reichek N, Willenbrock R, Zannad F, Phillips RA, Roniker B, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. Circulation. 2003 Oct;108(15): 1831–8.
17. Verdecchia P, Sleight P, Mancia G, Fagard R, Trimarco B, Schmieder RE, et al. Effects of telmisartan, ramipril, and their combination on left ventricular hypertrophy in individuals at high vascular risk in the ongoing telmisartan alone and in combination with ramipril global end point trial and the telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease. Circulation. 2009 Oct;120(14): 1380–9.
18. Solomon SD, Appelbaum E, Manning WJ, Verma A, Berglund T, Lukashevich V, et al. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. Circulation. 2009 Feb;119(4):530–7.
19. Liebson PR, Grandits GA, Dianzumba S, Prineas RJ, Grimm RH Jr, Neaton JD, et al. Comparison of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). Circulation. 1995 Feb;91(3):698–706.
20. Ernst ME, Neaton JD, Grimm RH Jr, Collins G, Thomas W, Soliman EZ, et al. Long-term effects of chlorthalidone versus hydrochlorothiazide on electrocardiographic left ventricular hypertrophy in the multiple risk factor intervention trial. Hypertension. 2011 Dec;58(6):1001–7.
21. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med. 2003 Jul;115(1):41–6.
22. Szwejkowski BR, Gandy SJ, Rekhraj S, Houston JG, Lang CC, Morris AD, et al. Allopurinol reduces left ventricular mass in patients with type 2 diabetes and left ventricular hypertrophy. J Am Coll Cardiol. 2013 Dec;62(24):2284–93.
23. Schmieder RE, Messerli FH, Garavaglia GE, Nunez BD. Dietary salt intake. A determinant of cardiac involvement in essential hypertension. Circulation. 1988 Oct;78(4):951–6.
24. MacMahon SW, Wilcken DEL, Macdonald GJ. The effect of weight reduction on left ventricular mass. A randomized controlled trial in young, overweight hypertensive patients. N Engl J Med. 1986 Feb;314(6):334–9.
25. Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. Circulation. 1994 Oct;90(4): 1786–93.
26. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, et al. Prognostic significance of serial changes in left ventricular mass in essential hypertension. Circulation. 1998 Jan;97(1):48–54.
27. Verdecchia P, Angeli F, Borgioni C, Gattobigio R, de Simone G, Devereux RB, et al. Changes in cardiovascular risk by reduction of left ventricular mass in hypertension: a meta-analysis. Am J Hypertens. 2003 Nov;16(11 Pt 1):895–9.
28. Devereux RB, Wachtell K, Gerdts E, Boman K, Nieminen MS, Papademetriou V, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA. 2004 Nov;292(19): 2350–6.
29. Okin PM, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Lindholm LH, et al. In-treatment resolution or absence

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

FOR CITATION PURPOSES: *Pokharel P, Bella JN.* Regression of left ventricular hypertrophy: lessons from clinical trials. OA Evidence-Based Medicine 2013 Nov 30;1(2):13.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Evidence-Based Medicine
Open Access

of electrocardiographic left ventricular hypertrophy is associated with decreased incidence of new-onset diabetes mellitus in hypertensive patients: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study. Hypertension. 2007 Nov;50(5):984–90.
30. Wachtell K, Palmieri V, Olsen MH, Gerdts E, Papademetriou V, Nieminen MS, et al. Change in systolic left ventricular performance after 3 years of antihypertensive treatment: the Losartan Intervention for Endpoint (LIFE) study. Circulation. 2002 Jul;106(2):227–32.
31. Bella JN, Goring HH. Genetic epidemiology of left ventricular hypertrophy. Am J Cardiovasc Dis. 2012;2(4):267–78.

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

FOR CITATION PURPOSES: *Pokharel P, Bella JN.* Regression of left ventricular hypertrophy: lessons from clinical trials. OA Evidence-Based Medicine 2013 Nov 30;1(2):13.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.