Prevention and treatment of hypertensive left ventricular hypertrophy

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Purpose of review
Left ventricular (LV) hypertrophy (LVH) is a well recognized target organ adaptation to longstanding uncontrolled hypertension and other cardiovascular risk factors. It is also a strong and independent predictor of many cardiovascular disorders.

Recent findings
This focused review explores the current concepts in screening, diagnosis, prevention, and treatment of LVH in patients with hypertension. Currently, the primary screening and diagnostic tools for LVH are ECG and 2D echocardiography. Implementing machine learning in the diagnostic modalities can improve sensitivity in the detection of LVH. Lifestyle modifications, blood pressure control with antihypertensive therapy, and management of comorbidities aid in preventing and reversing LV remodeling.

Summary
LVH is a common and often silent complication of hypertension. Prevention and reversal of LV remodeling are crucial for cardiovascular risk reduction in patients with hypertension.

Keywords
antihypertensives, ECG, echocardiography, hypertension, left ventricular hypertrophy

INTRODUCTION

Left ventricular (LV) hypertrophy (LVH) is a well recognized target organ adaptation to longstanding uncontrolled hypertension and other cardiovascular risk factors. In addition, it is a strong and independent predictor of many cardiovascular disorders (CVD), including ischemic heart disease, heart failure (HF), stroke, arrhythmias, and CVD mortality [1]. Several modifiable and nonmodifiable risk factors contribute to the development of LVH, including age, gender, genetic factors, hypertension, diabetes, obesity, chronic kidney disease (CKD), metabolic syndrome, obstructive sleep apnea, sedentary lifestyle, and dietary salt intake [2]. Based on the population characteristics and criteria used to define LVH, its prevalence can range between 36 and 77% in patients with hypertension [3]. Notably, ethnicity does play a prominent role in LVH, with one study showing a four-fold increase in the incidence of LVH in black patients compared to white patients, even after adjusting for confounding factors such as age, systolic blood pressure (BP), and body weight [4,5].

LV geometry is usually categorized into four groups based on LV mass indexed by body-surface area (LVMi) and relative wall thickness (RWT): normal geometry, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy. Concentric LVH is defined as increased LVMi and RWT, while eccentric hypertrophy refers to increased LVMi due to cavity dilation and normal RWT (Fig. 1) [6].

The relationship between hypertension and LVH is well established in the literature. Even in children, there is a strong relationship between hypertension and LVH, as shown in a meta-analysis demonstrating more than a fourfold increase in the risk of LVH in children with elevated ambulatory BP [7]. A recent large retrospective study with nearly 40 000 adult patients from the UK demonstrated a significant association between hypertension and concentric LVH assessed by cardiac MRI [8]. As

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Curr Opin Cardiol 2024, 39:251–258
DOI:10.1097/HCO.0000000000001135

KEY POINTS

- Left ventricular hypertrophy (LVH) is a well recognized target organ adaptation to longstanding uncontrolled hypertension and other cardiovascular risk factors and is a strong and independent predictor of many cardiovascular disorders.
- ECG and 2D echocardiography are the standard modalities for screening and diagnosing LVH. However, other methods, such as cardiac MRI, 3D echocardiography, and echocardiographic strain analysis, can help better characterize the LV geometry.
- Modern developments in machine learning promise increased sensitivity of ECG in diagnosing LVH.
- Lifestyle interventions such as diet modifications, weight loss, and exercise aid in preventing LVH, as does aggressive blood pressure control with antihypertensive medications.
- Treatment of comorbid conditions such as type 2 diabetes, chronic kidney disease, and obesity also has synergistic effects on the prevention and reversal of LVH.

expected, uncontrolled BP and longer duration since the diagnosis of hypertension were independent predictors of higher LVMi.

Development of LVH is a silent process, and patients often remain asymptomatic until the onset of diastolic dysfunction and elevated filling pressures. Therefore, early identification of patients with LVH is essential for timely interventions to prevent remodeling or halt progression. This focused review explores the current concepts in screening, diagnosis, prevention, and treatment of LVH in patients with hypertension (Fig. 2).

SCREENING AND DIAGNOSIS OF LEFT VENTRICULAR REMODELING IN HYPERTENSION

Hypertension is a leading cause of death and morbidity. Thus, the US Preventive Services Task Force recommends regular screening for hypertension in adults [9]. Diagnosis and management of hypertension require proper measurement in the office and ambulatory settings [10]. Moreover, a recent review demonstrated that hypertensive response to

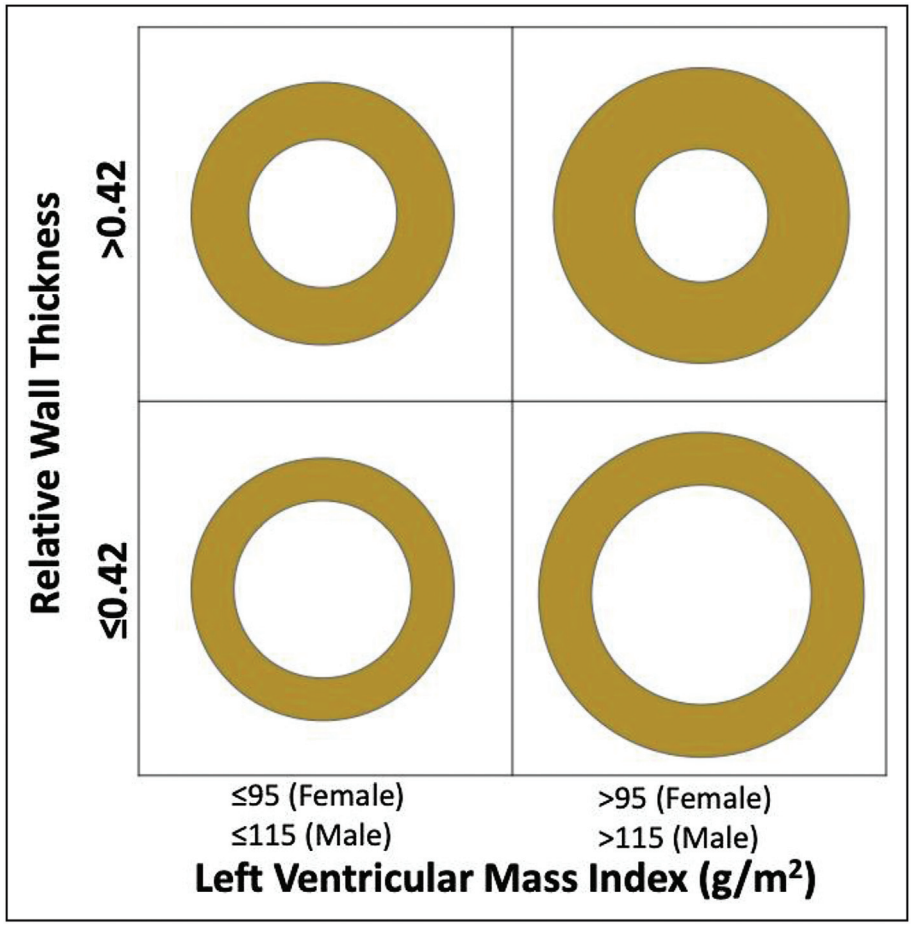

FIGURE 1. This illustration depicts left ventricular hypertrophy as defined by left ventricular mass index and relative wall thickness.

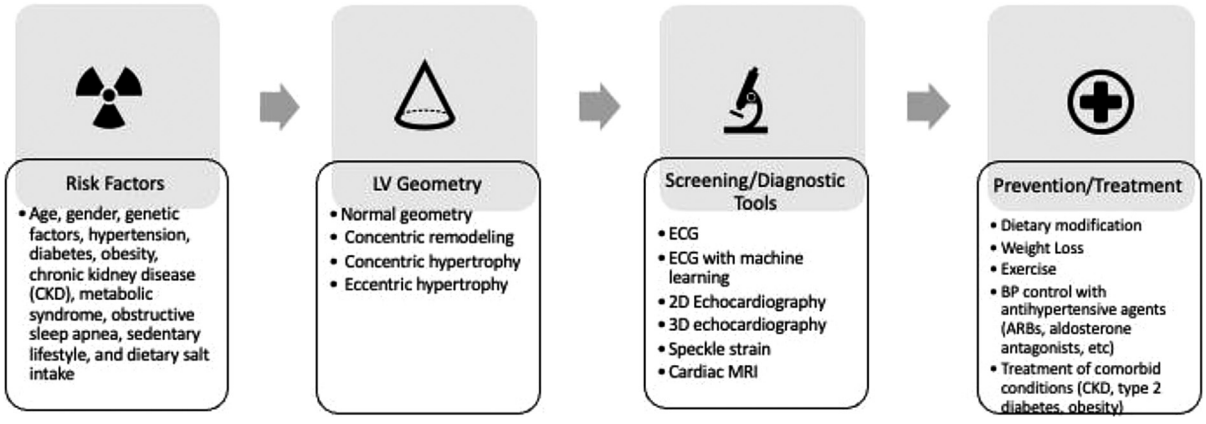

FIGURE 2. Central figure. The central illustration of the relationship between hypertension and left ventricular hypertrophy via risk factors, left ventricular geometry, screening/diagnostic tools, and prevention/treatment.

exercise during stress test, a potential marker for masked hypertension, is a strong predictor of LVH and other forms of hypertension-mediated organ damage [11].

Electrocardiogram (ECG) and 2D echocardiography are the primary tools for screening and diagnosing LVH, while cardiac MRI is considered the 'gold-standard' imaging for evaluating LV geometry and myocardium. Other cardiac imaging modalities such as cardiac computed tomography, PET, and SPECT provide information about LV geometry, although they are typically not utilized for evaluating LVH in clinical practice [12▪]. The most recent European Society of Hypertension guidelines recommend using ECG to screen for LVH in all hypertensive adults and echocardiography in the context of a more advanced diagnostic workup when hypertension-mediated organ damage is suspected [13▪▪].

Various ECG criteria exist for diagnosing LVH, most of which rely on increased voltage on different ECG leads [13▪▪]. With the rise of artificial intelligence, there has been an increased interest in examining the utility of deep learning or machine learning in the early identification of LVH through ECG. Although this field is still growing, promising results have shown that machine-learning models may be more sensitive in the early detection of LVH than our current clinical criteria (Table 1) [14,15]. Deep learning models are being utilized to extract valuable features that may not be distinguishable to the human eye [15].

Echocardiography remains one of the most accessible tools to diagnose and characterize LVH [18]. Compared to ECG, echocardiography is more sensitive in detecting LVH and provides a more comprehensive evaluation of LV geometry [13▪▪]. However, LVH diagnosis by ECG or echocardiography has similar prognostic value, as a recent retrospective report from the Korean Hypertension Cohort study shows. Notably, echocardiography provided additional prognostic risk stratification in patients without LVH on ECG [19].

The diagnostic value of echocardiography in evaluating LV remodeling has improved with advances in 3D echocardiography [18] and longitudinal strain analysis by speckle tracking [12▪,20]. Longitudinal strain analysis can assist with differentiating hypertensive heart disease from athlete's heart or hypertrophic cardiomyopathy [21]. LV global longitudinal strain (GLS) is typically more within the normal range in athletes than in patients with LVH secondary to hypertrophic cardiomyopathy and hypertension [22]. Furthermore, abnormal GLS and its deterioration in subsequent echocardiograms have been associated with major adverse cardiac events (MACE) in patients with hypertensive LVH [21,23].

PROGNOSTIC SIGNIFICANCE OF LEFT VENTRICULAR REMODELING IN HYPERTENSION

LV remodeling, which initially begins as an adaptive response, eventually increases the risk of cardiovascular complications in patients with hypertension [10]. Primarily, it predicts CVD morbidity and mortality as well as all-cause mortality, as evidenced by the landmark Framingham study in 1990, and has been replicated in literature ever since [24,25▪▪]. A recent report from a population-based prospective cohort study of 990 subjects without LVH at baseline demonstrated a significant independent association between an increase in echocardiographic LVMi and cardiovascular mortality over 18.5 years of follow-up [25▪▪]. More specifically, LVH is associated with HF, regardless of the ejection fraction subtype [26,27].

Table 1. Selection of recent publications that evaluate artificial intelligence in the diagnosis of LVH

Publication	Year	Subject size	AI modality	Confirmatory cardiac test	Main findings
Detection of Left Ventricular Hypertrophy Using Bayesian Additive Regression Trees: The MESA [16]	2019	4714 participants	BART (Bayesian additive regression trees)	12-lead ECG and cMRI pair	BART-LVH criteria are superior to traditional ECG-LVH criteria in predicting LV mass using cardiac MRI (cMRI) as the standard. BART-LVH also has a similar prognostic value compared to cMRI-LVH.
Automatic Detection of Left Ventricular Dilatation and Hypertrophy from Electrocardiograms Using Deep Learning [15]	2022	18 954 patients	Ensemble neural network (ENN), convolutional neural network (CNN), deep neural network (DNN) with raw ECG data as input	12-lead ECG and TTE pair	ENN, or deep learning models, were better at detecting LV dilatation than machine learning or conventional models.
Machine learning models of 6-lead ECGs for the interpretation of left ventricular hypertrophy (LVH) [14]	2023	250 000 ECGs from an extensive database	Binary class Random Forest (RF) models and DNN	6-lead ECG (limb leads)	DNN is superior to RF models. DNN models are similar when utilizing six leads (limb leads only) and 12-lead, suggesting potential clinical utility in developing mobile devices for 6-lead ECG.
Deep Learning Models for Predicting Left Heart Abnormalities From Single-Lead Electrocardiogram for the Development of Wearable Devices [17]	2024	229 439 ECG-echocardiogram pairs from multicenter data set	Convolutional neural network (CNN)	12-lead ECG	This deep learning model effectively predicts left ventricular abnormalities based on lead I alone from a 12-lead ECG and is superior to traditional methods in predicting LVH.

BART, Bayesian additive regression trees; cMRI, cardiac magnetic resonance imaging; CNN; TTE, transthoracic echocardiography; DNN, deep neural network; ENN, ensemble neural network; RF, random forest.

LIFESTYLE INTERVENTION FOR PREVENTION OF LEFT VENTRICULAR REMODELING

Many aspects of lifestyle intervention have been studied in the prevention and treatment of LVH through addressing diet, exercise, weight loss, stress reduction, and improved control of other comorbid conditions such as diabetes.

Dietary modification

Increased salt intake is a well understood risk factor for uncontrolled hypertension. A recent meta-analysis showed significant improvement in BP with sodium restriction (sodium intake $\leq$ 2400 mg/day) [28]. In a prospective cohort study, a high dietary sodium/potassium ratio at baseline was associated with higher LVMi [29]. Furthermore, a reduction in dietary salt may also result in reversal of LVH [28,30]. Although it is almost universally agreed upon that salt restriction aids BP control, current guidelines do not specify the recommended daily consumption [13▪▪]. Dietary vitamin D3 has also been explored as a possible intervention to reduce LVH. However, investigational studies failed to show any benefit of vitamin D3 on cardiac structure or function [31,32].

Weight loss

In patients with obesity, the etiology of LVH is thought to be multifactorial, with synergistic effects from hypertension, body mass, and nocturnal hypoxemia [33]. While BP control can reduce LVH, one review notes that in patients with concomitant obesity, weight loss is also necessary to see the reversal of LVH [34].

Reduced-calorie diets have been investigated, though to a more limited degree. A small-size randomized controlled trial (RCT) investigated the effects of a reduced-carbohydrate or reduced-fat hypocaloric diet in patients who were overweight or obese. After six months, both groups showed a decrease in LVMi and systolic and diastolic BP [35].

Exercise

There is a complex relationship between exercise and LV geometry, as intense exercise is known to cause physiologic cardiac remodeling, often described as 'athlete's heart' [36]. Broadly, the difference between the LV remodeling seen in athletes and patients with hypertension is the absence or presence of fibrosis accompanying the LVH respectively. As such, physical activity as a measure to prevent pathologic LV remodeling is now widely

accepted. Physical activity can reduce systolic BP by various mechanisms, including changes in systemic vascular resistance, oxidative stress, arterial compliance, and modification of the renin–angiotensin–aldosterone system (RAAS) [37]. Furthermore, multiple studies have shown that regular aerobic exercise can improve LV mass in patients with hypertension [37].

CLINICAL MANAGEMENT FOR PREVENTION AND REVERSAL OF HYPERTENSIVE LEFT VENTRICULAR HYPERTROPHY

The treatment of hypertension with medications is effective in preventing LVH. In addition, the primary goals of clinical management for individuals with hypertensive LVH are reverse remodeling and the reduction of future CV risk. Multiple RCTs have confirmed LVH regression in response to BP lowering with medical therapy [38–40]. Moreover, observational studies and clinical trial data from the 2000s indicated that LVH regression with antihypertensive therapy was associated with a lower risk of HF and adverse cardiovascular events [40,41]. Consistently, a 2022 meta-analysis including 1140 hypertensive patients found a significant reduction in LVMi in response to antihypertensive therapy. In addition, LVMi reduction was associated with improved GLS by speckle-tracking echocardiography, likely contributing to an overall improvement in LV function [42]. Furthermore, meta-analyses have shown that regression of LVH may be associated with a reduction in CVD risk [43,44].

Dedicated RCTs have not evaluated BP targets for patients with hypertensive LVH. However, a retrospective nationwide study including 95545 Korean adults with LVH by ECG revealed that SBP <130 and DBP <80 carried the lowest risk for CVD events over a median follow-up of 11.5 years [45]. This finding is in contrast to a posthoc analysis involving hypertensive patients from a clinical trial, in which those with ECG-LVH experienced higher cardiac mortality and all-cause mortality when an SBP <130 mmHg was achieved with therapy, compared to a higher BP target [46].

The guideline-directed first-line antihypertensive agents effectively prevent and reverse LVH [47]. However, the RAAS overactivation plays a significant role in LV remodeling. Agents targeting RAAS (angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists) appear more effective in LVH regression than other agents [48,49]. Evidence from clinical trials and meta-analyses in the 2000s demonstrated that therapy with ARBs led to a more significant reduction in LV mass than beta blockers [50]. More recent evidence confirmed the superiority of sacubitril-valsartan over ARBs in LV reverse remodeling in patients with hypertension [51]. An RCT including 114 patients with hypertension compared the impact of sacubitril-valsartan versus olmesartan on LV geometry assessed by cardiac MRI. After nearly a year of therapy, patients assigned to the sacubitril-valsartan group achieved a more significant reduction in LVMi, even after adjustment for changes in SBP [52].

Aldosterone itself mediates LV remodeling and dysfunction. Therefore, primary hyperaldosteronism evaluation may be warranted in patients with early-onset or resistant hypertension. Treatment with medical therapy, such as aldosterone antagonists, or surgical therapy, such as adrenalectomy, can improve LV remodeling and dysfunction in these patients [53].

Patients with renal artery stenosis commonly have resistant hypertension, and they are at high risk of hypertensive LVH, attributable to a marked elevation in angiotensin II and aldosterone caused by decreased renal perfusion [54]. A meta-analysis including 726 patients with renal artery stenosis found that renal revascularization significantly reduced echocardiographic LVMi and was associated with a 40% lower LVH risk [55].

Despite effective BP control, specific clinical characteristics render patients more susceptible to persistent LVH. This finding was noted in a population-based cohort study including 2173 hypertensive patients with asymptomatic LVH. After a median follow-up period of 67 months, only 14% of patients achieved definitive LVH regression despite optimal BP achieved in 87% of participants [56]. The phenotype of patients who did not confer LVH regression was typically older and had a longer duration of hypertension, established end-organ damage, higher values of LVMi, and higher rates of obesity. A similar longitudinal study involving the Strong Heart Study participants also found that a lack of decrease in LVMi was associated with older age and central obesity [57]. These findings highlight the importance of early and effective treatment of BP and associated comorbidities in patients with hypertension.

Over the past years, the definition and management of hypertensive heart disease have evolved beyond LV dimensions and BP control. Furthermore, there has been a call for a more sophisticated approach, such as implementing multimodality imaging, monitoring and targeting biomarkers, and utilizing machine learning and artificial intelligence [58▪]. A recent ancillary study involving 8820 participants of the Systolic Blood Pressure Intervention

Trial (SPRINT) compared outcomes of patients based on ECG-LVH status and cardiac biomarker levels. Patients with LVH and elevated high-sensitivity cardiac troponin T (≥14 ng/l) or N-terminal pro-B-type natriuretic peptide (≥125 pg/ml) at baseline were defined as 'malignant' LVH. 'Malignant' LVH phenotype was associated with a 4-fold higher risk of HF and all-cause mortality. In comparison, LVH with negative biomarkers was associated with a 2-fold higher risk than those without LVH or biomarker elevation [59▪]. Intensive BP control led to a similar relative risk reduction regardless of LVH or biomarker status. However, those with 'malignant' LVH experienced a greater absolute risk reduction due to elevated risk at baseline.

Treatment of comorbid conditions

Commonly occurring comorbid conditions, such as chronic kidney disease (CKD), type 2 diabetes, and obesity, have synergistic effects with hypertension on causing LV remodeling [60,61]

In patients with hypertensive LVH and obesity, weight loss can be effective in reversing LV remodeling. An observational study involving patients with hypertension and obesity showed that weight loss after one year of follow-up was associated with a reduction in LVMi, independent of age and BP [62]. For patients unable to achieve weight loss solely on lifestyle changes, bariatric surgery effectively reduces LV mass and improves systolic function [63].

A meta-analysis involving studies reporting preoperative and postoperative cardiac indices per echocardiography or cardiac MRI found that patients undergoing bariatric surgery experienced, on average, an 11.2% reduction in LVMi [64]. Our literature search did not reveal any human studies exploring the impact of novel weight-loss agents (i.e., glucagon-like peptide-1 receptor agonists) on LV geometry.

In patients with diabetes and hypertension, ACE inhibitors are highly effective in preventing LVH [65]. There is also a heightened interest in the impact of antidiabetic agents on cardiac remodeling. Small dedicated RCTs involving patients with type-2 diabetes demonstrated that sodium/glucose cotransporter-2 inhibitor (i.e., empagliflozin or dapagliflozin) therapy can significantly reduce LVMi [66,67].

LVH in CKD is considered multifactorial due to increased afterload (with increased arterial stiffness due to hypertension, overactivation of RAAS, disordered bone metabolism, chronic inflammation), increased preload (hypervolemia, chronic anemia, arteriovenous fistulas), and various intrinsic factors (uremic toxins, oxidative stress, hyperparathyroidism, vitamin D deficiency) [61]. LVH indices strongly correlate with the stage of CKD [68]. Therefore, early recognition and treatment of CKD are essential for the prevention of CVD complications in patients with hypertension.

CONCLUSION

LVH is highly prevalent in patients with hypertension. It initially begins as an adaptive response but eventually contributes to CVD morbidity and mortality. ECG and 2D echocardiography are the primary tools for screening and diagnosing LVH. Recent developments in machine learning offer improved sensitivity in the early detection of LVH by ECG. The primary goals of clinical management of hypertensive LVH are reverse remodeling and reducing future CV risk. Clinical management of patients with hypertensive LVH requires a comprehensive approach, including lifestyle modifications, intense blood pressure control with antihypertensive therapy, and appropriate management of comorbidities that synergistically contribute to LV remodeling.

Acknowledgements

None.

Financial support and sponsorship

No external funding.

Conflicts of interest

There are no conflicts of interest.

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- ▪▪ of outstanding interest

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