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Research Article

Importance of blood pressure control in left ventricular mass regression

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Abstract

Blood pressure (BP) reduction to 140/90 mm Hg or lower using renin-angiotensin-system blockers reportedly provides the greatest left ventricular (LV) mass regression; β-blockers have less effect. This study examined whether combination antihypertensive therapy would provide greater benefit. With a double-blind, parallel-group design, the effects of 3 different combinations, carvedilol controlled-release (CR)/lisinopril, atenolol/lisinopril, and lisinopril, on left ventricular mass index (LVMI) were assessed by MRI after 12 months. Patients were treated to achieve guideline-recommended BP ($<$140 mm Hg/$<$90 mm Hg; diabetes: $<$130 mm Hg/$<$80 mm Hg). Sample size was calculated to achieve 90% power to detect a 5 g/m^2 difference in mean change from baseline in LVMI between the carvedilol CR/lisinopril group and each of the other treatment groups. Of 287 patients randomized, more than 50% were titrated to maximum dosage; 73% reached targeted BP. At month 12 (last observation carried forward $\geq$ month 9) for 195 evaluable subjects, mean BP was similar in all groups (carvedilol CR/lisinopril: 128.8/77.9; atenolol/lisinopril: 128.7/76.5; lisinopril: 126.3/80.3 mm Hg). Compared with baseline, mean LVMI decreased to a similar extent in all groups (carvedilol CR/lisinopril: –6.3; atenolol/lisinopril: –6.7; lisinopril: –7.9 g/m^2). **A**chievement of targeted BP control is more important than treatment regimen in achieving LV mass reduction. J Am Soc Hypertens 2010;4(6):302–310.

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Introduction

In patients with hypertension, left ventricular hypertrophy (LVH) is a strong predictor of cardiovascular morbidity and mortality.[1–3] LVH significantly increases the risk of coronary artery disease and congestive heart failure as well as the risk of adverse cardiovascular events including myocardial infarction, stroke, and sudden death.[4–7] Further, a direct relationship has been demonstrated between absolute LV mass and cardiovascular risk.[1] Patterns of LV remodeling characteristic of LVH associated with hypertension include the following: compensatory thickening of the ventricular wall to normalize wall stress with progressive increase in LV mass (concentric hypertrophy); increased wall thickness

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with reduced LV volume and normal LV mass (concentric remodeling); and increased LV mass and volume (eccentric hypertrophy).[8] Such remodeling often leads to decreased LV compliance and impaired LV diastolic filling.[9] Moreover, abnormal accumulation of fibrillar collagen is associated with LV diastolic dysfunction, whereas development of hypertensive heart disease leads to a transition of cardiac fibroblasts to myofibroblasts that modify the extracellular matrix.[10] Chronic activation of the renin-angiotensin-aldosterone system also serves to increase extracellular matrix fibrillar collagen.[11]

LV mass regression is associated with improved cardiovascular outcomes,[12,13] and treatment goals for lowering blood pressure (BP) should lead to regression of LVH.[14] A meta-analysis of more than 100 studies indicated a moderately strong relationship between BP reduction and LV mass regression.[15] Sustained BP reduction has been shown to have continued reductions in echocardiographic LV mass over 2 years.[16] Over 3 to 5 years, the lowering of BP to approximately 140/90 mm Hg can prevent progression to severe hypertension and the development of LVH and congestive heart failure.[17] Currently, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), commonly in combination with diuretics, are considered the first-line therapy for hypertensive patients with LVH.[18–22]

Conventional β-adrenoreceptor antagonists (β-blockers) are not known to reduce LV mass to the same degree as renin-angiotensin-aldosterone system (RAAS) blockers when systolic BP is well above 130 mm Hg.[23] Nonselective β-blockers with α-adrenergic blocking activity elicit vasodilation and should reduce afterload, further contributing to LV mass regression.[24] In studies in hypertensive patients,[25,26] carvedilol immediate-release (IR) has demonstrated reductions in left ventricular mass index (LVMI). β-blockers in combination with an ACE inhibitor have not been previously evaluated in patients with hypertension and LVH in whom BP was controlled to goal levels. Neither the single agents nor their combination has been studied when systolic BP was reduced to lower than 130 mm Hg. The CLEVER study (a randomized, double-blind, multicenter study comparing the effects of carvedilol controlled-release [CR] formulation and atenolol in combination with and compared with an ACE inhibitor [lisinopril] on LV mass regression in hypertensive patients with LVH) represents the first parallel-group trial to compare the effects of appropriately titrated dosages of carvedilol CR in combination with the ACE inhibitor lisinopril, with those of the selective β_1-adrenergic receptor blocker atenolol in combination with lisinopril and those of lisinopril alone without β-blockade. The reduction in left ventricular mass was evaluated both by magnetic resonance imaging (MRI) and echocardiography after patients were titrated to guideline-recommended target BP and maintained on therapy for 12 months.

Methods

This study was conducted in 46 centers in the United States following approval by Institutional Review Boards and in accordance with the ethical principles of the Declaration of Helsinki. All participants gave written informed consent.

Study Population

Enrolled participants were men and women 18 to 80 years of age with Stage I or II hypertension and LVH. Nondiabetic subjects with a documented history of hypertension controlled by 2 or more antihypertensive medications (<maximal doses of ≥3 medications), a mean sitting systolic blood pressure (sSBP) lower than 140 mm Hg, and a mean sitting diastolic blood pressure (sDBP) lower than 90 mm Hg (diabetic: sSBP <130 mm Hg and sDBP <80 mm Hg) at screening were eligible. Additionally, nondiabetic subjects uncontrolled on 1 or 2 antihypertensive medications (<maximal doses of 2 medications) or subjects untreated or newly diagnosed with an sSBP of 140 or higher and 179 or lower mm Hg and/or an sDBP of 90 or higher and 109 or lower mm Hg (diabetic: sSBP ≥130 and ≤179 mm Hg and/or sDBP ≥80 and ≤109 mm Hg) were also eligible. At prescreening, the presence of LVH was evaluated by 2-dimensional echocardiography with Doppler imaging. Subjects were eligible if one of the following criteria was met: LVMI 110 g/m^2 or higher for females or 134 g/m^2 or higher for males with LV mass indexed by body surface area[8] or LV mass indexed to height higher than 41 g/m$^{2.7}$ for females or 52 g/m$^{2.7}$ or higher for males with LV mass indexed to height.[27]

Major exclusion criteria included LVH not related to essential hypertension, uncontrolled diabetes mellitus (HbA1c >9%), significant coronary artery disease, second- or third-degree heart block, myocardial infarction or stroke within 3 months of screening, congestive heart failure (New York Heart Association [NYHA] class II–IV), hepatic impairment, and renal insufficiency (creatine clearance [CrCL] ≤25 mL/min). β_2-adrenergic agonists and other antihypertensive medications not specified by the protocol were not allowed.

Study Design

This was a randomized, double-blind, parallel-group study to compare the effects of carvedilol CR (20, 40, or 80 mg), atenolol (50, 75, or 100 mg), and lisinopril (10, 20, or 40 mg), each administered once daily, in combination with open-label lisinopril 20 mg once daily on LV mass regression during 12 months of treatment.[28]

After discontinuing previous antihypertensive medications, eligible subjects entered the 2-week run-in and received lisinopril 10 mg once daily for 1 week followed