

# Hypertension and left ventricular hypertrophy: how much attention should we pay to the renin-angiotensin-aldosterone system?

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*Left ventricular hypertrophy (LVH) is an important independent cardiovascular risk factor. Angiotensin II and aldosterone, the effectors of the renin-angiotensin-aldosterone system (RAAS), have been found to increase LVH in a blood-pressure-independent fashion in several animal models of RAAS activation and in observational studies in humans. Pharmacological interventions interacting with the RAAS, namely, angiotensin-converting enzyme inhibition, blockade of the angiotensin II type 1 receptor, and antagonism at the mineralocorticoid receptor, have been shown to reduce LVH. These beneficial effects are in addition to, and independent from, their blood pressure-lowering properties and improve cardiovascular prognosis. The main question to be answered in the future is which combination of drugs interfering with the RAAS will prove to be most beneficial.*

**Keywords:** hypertension; left ventricular hypertrophy; risk factor; RAAS; angiotensin II; ACE inhibition; prognosis

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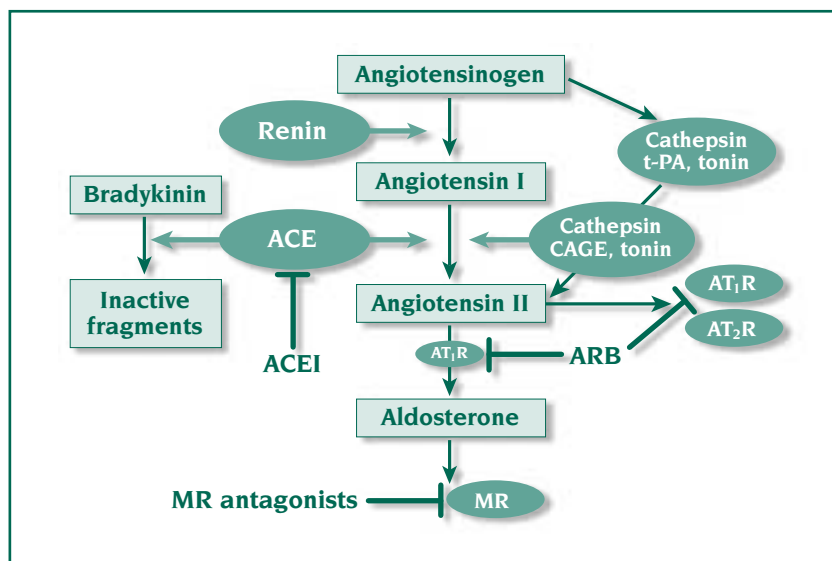
**L**eft ventricular hypertrophy (LVH) has been shown to be an important independent risk factor for cardiovascular morbidity and mortality.<sup>1</sup> It also has been proposed that correction of LVH reduces the associated elevated cardiovascular risk.<sup>2,3</sup> Therefore, reduction of LVH is one important goal of antihypertensive treatment. This raises the question of whether all antihypertensive medications are similarly effective or whether some are superior with regard to reduction in LVH. The aim of this review is to define how important a role the renin-angiotensin-aldosterone system (RAAS) plays in the development of LVH and to which extent drugs blocking the RAAS can achieve regression of LVH.

## PHYSIOLOGY AND PHARMACOLOGY OF THE RAAS

*Figure 1 (page 34) shows the well-known cascade of the RAAS. The physiological function of the RAAS is to regulate blood pressure and to maintain salt and water homeostasis. The principal effectors of the system are angiotensin II and aldosterone. Angiotensin II is a potent vasoconstrictor and has profibrotic, hypertrophy-inducing, and growth-promoting effects on the heart as well as other organs. It exerts its effects through (at least) two receptors: the angiotensin II type 1 receptor (AT<sub>1</sub>) and type 2 receptor (AT<sub>2</sub>). The main effects of angiotensin II are mediated by the AT<sub>1</sub> receptor.*

### SELECTED ABBREVIATIONS AND ACRONYMS

<b>4E-LVH</b>	Eplerenone, Enalapril and Eplerenone/Enalapril-Left Ventricular Hypertrophy (study)
<b>ARB</b>	angiotensin receptor blocker
<b>AT<sub>1</sub>, AT<sub>2</sub></b>	angiotensin II type 1 (2) (receptor)
<b>LIFE</b>	Losartan Intervention For Endpoint reduction in hypertension
<b>LVH</b>	left ventricular hypertrophy
<b>LVMI</b>	left ventricular mass index
<b>MR</b>	mineralocorticoid receptor
<b>PIC<math>\gamma</math>EL</b>	Preterax In a double-blind Controlled study Versus Enalapril in Left ventricular hypertrophy
<b>RAAS</b>	renin-angiotensin-aldosterone system
<b>VALUE</b>	Valsartan Antihypertensive Long-term Use Evaluation



**Figure 1.** Schematic view of the renin-angiotensin-aldosterone system (RAAS) and possible pharmaceutical interventions.

**Abbreviations:** ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AT<sub>1</sub>R, angiotensin II type 1 receptor; AT<sub>2</sub>R, angiotensin II type 2 receptor; CAGE, chymostatin-sensitive angiotensin II-generating enzyme; MR, mineralocorticoid receptor; t-PA, tissue plasminogen activator.

Activation of the AT<sub>2</sub> receptor has been shown to be at least in part, and in some tissues completely, antagonistic to activation of the AT<sub>1</sub> receptor. Aldosterone regulates renal sodium handling and also exerts profibrotic effects on the heart, kidney, and blood vessels. It acts mainly via the mineralocorticoid receptor (MR), although nongenomic effects of aldosterone are also well described.<sup>4</sup>

Drugs blocking the RAAS include the angiotensin-converting enzyme (ACE) inhibitors, selective antagonists at the AT<sub>1</sub> receptor (ARBs, angiotensin receptor blockers), and antagonists at the MR (MR antagonists). The role of renin inhibitors is not further discussed, since at the moment orally active compounds are not available (though aliskiren may be, in the near future). The effects of these drug classes are similar, but clearly not identical. ACE inhibitors cause a decrease in angiotensin II levels and thereby decreased activity at the AT<sub>1</sub> and AT<sub>2</sub>

receptors, but they increase bradykinin levels. ARBs cause an increase in angiotensin II levels via a negative feedback loop, and therefore increase the activity at the AT<sub>2</sub> receptor. Higher bradykinin levels and activation of the AT<sub>2</sub> receptor are specific effects of ACE inhibitors and ARBs, respectively, which might contribute to the effect of either class in addition to RAAS blockade. This also means that ACE inhibitors and ARBs do not have identical pharmacological profiles.

Blockade of the MR only affects the actions of aldosterone, and leaves angiotensin II concentrations unchanged or even increased, whereas plasma aldosterone levels are increased. This, in turn, could promote nonclassic effects of aldosterone.

The pharmacological differences between these drug classes are one reason why combination of different drug classes might be more effective than monotherapy. Another reason for combining various RAAS block-

ing drugs is that, over time, ACE-inhibitor blockade of the RAAS might become incomplete, leading to a loss of suppression of aldosterone plasma levels. This phenomenon is called aldosterone escape and occurs in about one third of patients treated with ACE inhibitors, and thus limits their effectiveness.

In the following sections, we discuss the evidence from experimental studies, observational human data, and clinical trials confirming the role of the RAAS in inducing LVH.

### RAAS AND LVH: EXPERIMENTAL EVIDENCE

There is strong evidence from cell culture and animal experiments that angiotensin II exerts profibrotic, hypertrophy-inducing, and growth-inducing effects, which cause hypertrophy of the left and right ventricles. The mechanisms by which angiotensin II causes these effects are complex and still the subject of intensive research. These effects appear to mainly result from, among others, an increase in transforming growth factor  $\beta$  (TGF $\beta$ ) production,<sup>5</sup> the activation of myocardial calcineurin,<sup>6</sup> and an increase in intracellular calcium.<sup>7</sup> Although these effects seem to be mediated by the AT<sub>1</sub> receptor,<sup>8</sup> conflicting findings have also been reported.<sup>9</sup>

With regard to aldosterone, chronic elevation of aldosterone levels combined with sodium intake induces myocardial fibrosis in rat left and right ventricles. The observation that fibrosis takes place even in the right ventricle argues for the concept that the fibrotic processes are blood pressure-independent.<sup>10,11</sup> Furthermore, it has been proposed that aldosterone causes fibrosis and hypertrophy by interaction with angiotensin II. It has been shown in aldosterone-salt-treated rats that



aldosterone increases AT<sub>1</sub> receptor mRNA and the ventricular density of the AT<sub>1</sub> receptor. Robert et al showed that myocardial fibrosis was almost blunted to the same extent by ARBs as by spironolactone.<sup>12</sup>

### RAAS AND LVH: OBSERVATIONAL HUMAN DATA

#### Renal artery stenosis

Renal artery stenosis causes excessive renin release from the macula densa, which causes activation of the RAAS, leading to an increase in circulating angiotensin II and aldosterone. Accordingly, patients with renovascular hypertension have pronounced hypertensive end-organ damage when compared with patients with essential hypertension. In one study, 32.6% of patients with renovascular hypertension exhibited LVH, in contrast to only 10.8% of patients with essential hypertension.<sup>13</sup>

#### Primary hyperaldosteronism

Primary hyperaldosteronism is characterized by elevated aldosterone levels accompanied by suppressed renin and angiotensin II, thus excluding significant concurrent effects of angiotensin II. In a cross-sectional study, LVH was shown to be more pronounced and to precede other organ damage, eg, of eyes or kidneys, in patients with primary hyperaldosteronism, compared with patients with essential hypertension.<sup>14</sup>

Patients with Conn's adenoma exhibited a greater left ventricular mass and relative wall thickness than patients with essential hypertension matched for other confounding determinants of left ventricular mass.<sup>15</sup> In parallel with the exaggerated concentric left ventricular remodeling and mass, these patients were characterized by an impaired

diastolic filling of the left ventricle. These studies therefore suggest a blood pressure-independent effect of aldosterone on left ventricular structure and function.

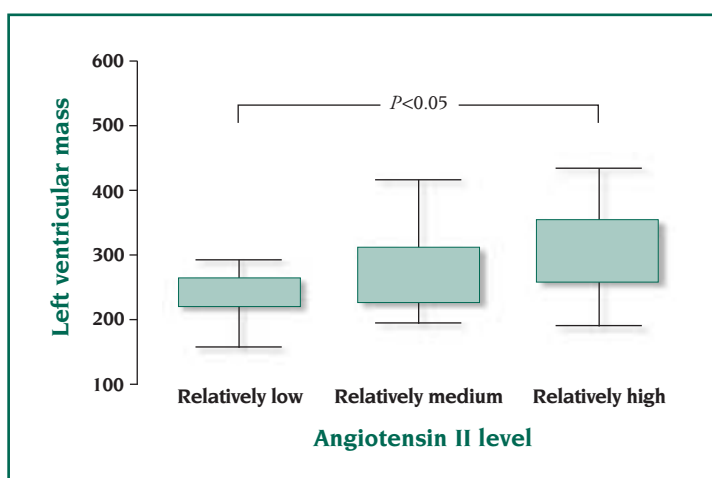
#### Essential hypertension

In essential hypertension, a connection between angiotensin II as well as aldosterone and LVH has been repeatedly documented. In 68 otherwise healthy untreated young mildly hypertensive men, we showed that patients with angiotensin II levels high with respect to the corresponding urinary salt excretion had greater left ventricular mass than patients with relatively low angiotensin II levels (*Figure 2*).<sup>16</sup> Since high sodium intake suppresses the activity of the RAAS, our results sug-

gest that a different reactivity of the RAAS in concert with an increased salt intake is responsible for the development of LVH in essential hypertension. It has been reported that in patients with essential hypertension serum aldosterone levels are closely related to left ventricular mass after correction for the effects of blood pressure.<sup>17</sup> In a cohort of hypertensive patients of young age and with only mild hypertension, a close relationship between urinary aldosterone excretion during high salt intake and left ventricular mass was consistently demonstrated.<sup>18</sup>

#### Genetic polymorphisms of the RAAS

Several linkage studies have been performed trying to link polymorphisms of genes of the RAAS to hypertension and hypertensive end-organ damage, especially LVH. In a study in 120 normotensive and mildly hypertensive young men, it was shown that hypertensive subjects with the -344 CC genotype of the aldosterone synthase promoter had a



**Figure 2.** Left ventricular mass in mildly essential hypertensive patients with relatively high angiotensin II levels for their salt intake was significantly higher than in patients with relatively low angiotensin II levels for their salt intake.

Modified from reference 16: Schmieder RE, Langenfeld MR, Friedrich A, Schobel HP, Gatzka CD, Weihprecht H. Angiotensin II related to sodium excretion modulates left ventricular structure in human essential hypertension. *Circulation*. 1996;94:1304-1309. Copyright © 1996, American Heart Association, Inc.

gest that a different reactivity of the RAAS in concert with an increased salt intake is responsible for the development of LVH in essential hypertension. It has been reported that in patients with essential hypertension serum aldosterone levels are closely related to left ventricular

greater left ventricular end-diastolic diameter and smaller relative wall thickness than those with the TT genotype. The latter showed a greater increase in urinary sodium excretion after oral sodium loading. Accordingly, suppression of aldosterone levels was found in hypertensive

subjects with the  $-344 TT$  and  $-TC$  genotype, but not in patients with the  $CC$  genotype. This suggests that decreased ability to suppress aldosterone levels on salt loading is linked with early eccentric left ventricular remodeling in hypertensives with the  $-344 CC$  genotype of the aldosterone synthase promoter.<sup>19</sup>

In a similar study, it could be shown that the  $+1675 G/A$ -polymorphism of the  $AT_2$  receptor is linked to LVH in young mildly hypertensive males.<sup>20</sup> Blood pressure levels as potential confounding factors were ruled out by including 24-hour ambulatory blood pressure into the analysis. The WHO-MONICA (World Health Organization–MONItoring trends and determinants in Cardiovascular diseases) study, a large epidemiological study in Augsburg, confirmed the link between  $AT_2$ -receptor polymorphism and the degree of LVH. Interestingly, this  $AT_2$ -receptor polymorphism has also been found to be a powerful prognostic marker for coronary heart disease.<sup>21</sup>

These and other studies suggest that polymorphisms modulating the activity of the RAAS influence left ventricular structure. Thus, these data support the view that activity of the RAAS is linked to LVH.

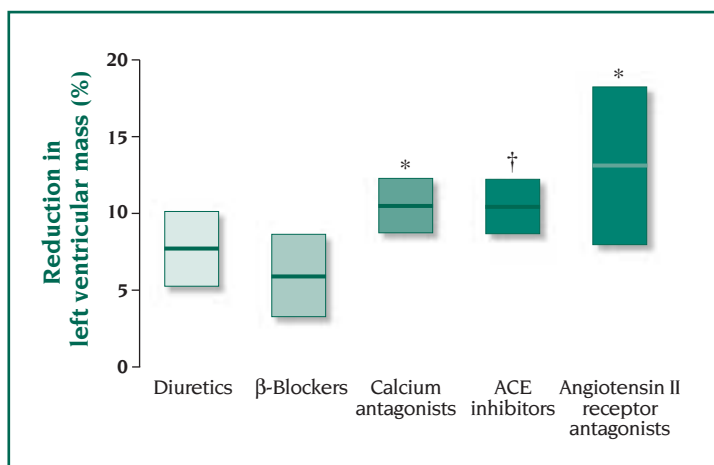
## RAAS AND LVH: THERAPEUTIC CLINICAL TRIALS

### Meta-analyses

Several meta-analyses have been performed, all of which consistently showed that drugs blocking the RAAS are superior to conventional antihypertensives with regard to reduction of LVH. The most recent meta-analysis, by Klingbeil et al,<sup>22</sup> included for the first time a larger amount of data from ARB trials. In this meta-analysis, 3767 patients

from 146 active treatment arms and 346 patients from 17 placebo arms were included. All studies were randomized, double-blinded, controlled, parallel group studies, using echocardiography for the diagnosis. Results were adjusted for blood pressure and treatment duration. Left ventricular mass index (LVMI) decreased by 13% with ARBs, by 11% with calcium antagonists, by 10% with ACEIs, by 8% with diuretics, and by 6% with  $\beta$ -blockers (Figure 3).<sup>22</sup> The difference in reduction of left

hypertension, the main inclusion criterion. During a mean follow-up of 4.8 years, 11% of losartan-treated and 13% of atenolol-treated hypertensive patients reached the composite primary end point (death, myocardial infarction, stroke), which reflects a 13% reduction in relative risk with losartan treatment.<sup>23</sup> Further analyses revealed that about one third of the benefit of losartan, compared with atenolol, was attributable to the greater reduction in LVH.



**Figure 3.** Meta-analysis of the efficacy of different antihypertensive drug classes in decreasing left ventricular mass. \* $P < 0.05$  vs  $\beta$ -blockers; † $P < 0.01$  vs  $\beta$ -blockers.

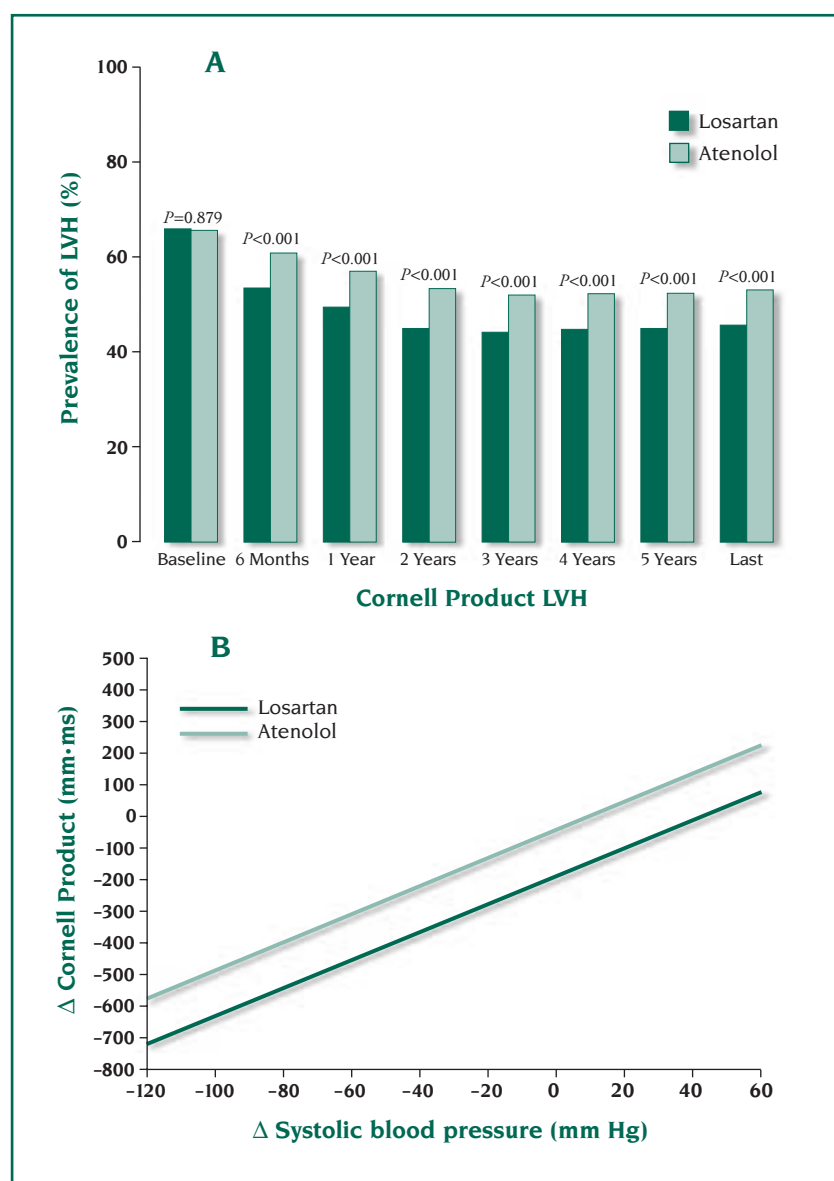
Modified from reference 22: Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med.* 2003;115:41-46. Copyright © 2003, Elsevier, Inc.

ventricular mass among the five antihypertensive drug classes was statistically significant ( $P = 0.004$ ). In pairwise comparison between drug classes, ARBs, calcium antagonists, and ACE inhibitors all reduced LVMI significantly more than  $\beta$ -blockers.

### The LIFE study

Losartan Intervention For Endpoint reduction in hypertension (LIFE) was a large-scale study in which 9193 patients were randomized to an either losartan- or atenolol-based antihypertensive regimen. The population was at high risk for cardiovascular events, since LVH was, besides

LVH was assessed by using ECG criteria. Losartan reduced the Cornell product by 10% and the Sokolow-Lyon index by 16%. The reductions were only 4% and 8%, respectively, in the atenolol-treated group. This effect became significant already 6 months after the start of treatment (Figure 4a).<sup>24</sup> Of note, this discrepant effect between losartan and atenolol was evident throughout the entire follow-up period of 4.8 years. In other words, the superiority of ARBs in reducing LVH does not diminish over time. Importantly, in this study, blood pressure was nearly identical in both treatment groups. Furthermore, analysis of regression lines



**Figure 4.** (A) Prevalence of left ventricular hypertrophy (LVH) during the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study as assessed by the Cornell product. (B) Blood pressure-independent effect of losartan versus atenolol of LVH in the LIFE trial shown by the downward shift of the  $\Delta$  Cornell product /  $\Delta$  blood pressure regression line.

Modified from reference 24: Okin PM, Devereux RB, Jern S, et al. Losartan Intervention for Endpoint reduction in hypertension Study Investigations. Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: the Losartan Intervention for Endpoint reduction in Hypertension (LIFE) Study. *Circulation*. 2003;108:684-690. Copyright © 2003, American Heart Association, Inc.

comparing changes in LVH clearly show the pressure independence of these effects (Figure 4b).<sup>24</sup> Therefore, the results of this study reflect a blood pressure-independent effect of RAAS blockade on LVH compared with  $\beta$ -blockade.

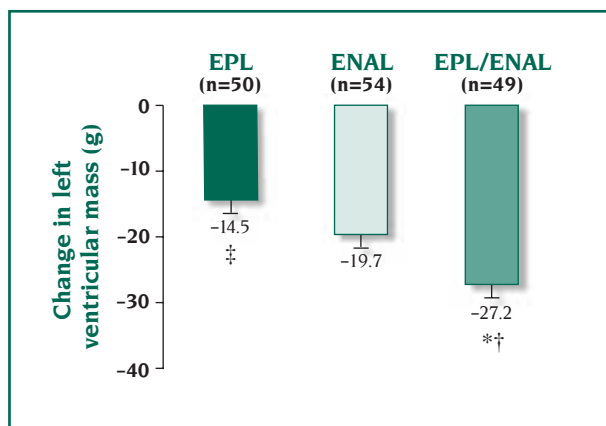
#### The 4E-LVH Study

In this small study (4E-LVH, Eplerenone, Enalapril and Eplerenone/Enalapril-Left Ventricular Hypertrophy study), monotherapy with enalapril 40 mg (n=54) or the new

MR antagonist eplerenone 200 mg (n=50) was compared with the combination of both (enalapril 10 mg, eplerenone 200 mg). Left ventricular mass was assessed by magnetic resonance imaging (MRI), which is able to assess changes in LVH with very high sensitivity. Eplerenone and enalapril reduced left ventricular mass similarly, by  $14.5 \pm 3.4$  g and  $19.7 \pm 3.2$  g, respectively. The combination therapy reduced left ventricular mass by  $27.2 \pm 3.4$  g. This decrease was significantly greater than with eplerenone alone ( $P=0.007$ ), whereas this difference was not significant ( $P=0.107$ ) compared with enalapril. These data suggest that combination therapy to block the RAAS might be more effective than just blocking single steps of the cascade (Figure 5, page 38).<sup>25</sup>

#### The PIC $\chi$ EL study

Low-dose combination therapy is a new therapeutic option for the first-line therapy of hypertension. The Preterax In a double-blind Controlled study Versus Enalapril in Left ventricular hypertrophy (PIC $\chi$ EL) study compared the effect on LVH regression of a low-dose combination of perindopril 2 mg and indapamide 0.625 mg with enalapril 10 mg monotherapy in a parallel group, double-blinded, randomized trial with 556 patients with LVH at baseline. To achieve blood pressure control, doses could be increased up to perindopril 8 mg and indapamide 2.5 mg or enalapril 40 mg. After an observation period of 52 weeks, perindopril/indapamide therapy had lowered LVMI by 13.6%, whereas enalapril alone had lowered LVMI by 3.9% only ( $P<0.001$ ). This greater LVMI reduction remained significant, even after adjustment for the greater blood pressure reduction obtained with the perindopril/indapamide combination versus enalapril.<sup>26,27</sup>



**Figure 5.** Change in left ventricular mass in the Eplerenone, Enalapril and Eplerenone/Enalapril– Left Ventricular Hypertrophy (4E-LVH) study. EPL = eplerenone, ENAL = enalapril; \*P<0.007 vs eplerenone; †P=0.107 vs enalapril; ‡P=0.258 vs enalapril.

Modified from reference 25: Pitt B, Reichek N, Willenbrock R, 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;108:1831-1838. Copyright © 2003, American Heart Association, Inc.

### The VALUE trial

Valsartan Antihypertensive Long-term Use Evaluation (VALUE) was a large-scale trial comparing the effects of valsartan and amlodipine on cardiovascular outcome in 15 245 hypertensive patients at high cardiovascular risk. This study failed to show a superiority of the ARB with regard to the combined cardiac end point and confirmed the beneficial effects on development of congestive heart failure, although the valsartan-treated group had a worse blood pressure control.<sup>28</sup> To date, no data about the effects of these two drugs on LVH are yet available. Furthermore, inadequate blood pressure control has been identified as a determinant of LVH in the VALUE trial.<sup>29</sup>

### CONCLUSION

There is now strong evidence for specific blood pressure-independent effects of angiotensin II and aldosterone on the myocardium. Thus, in patients with LVH, we should pay much attention to achieving adequate blockade of the RAAS.

The main question to be answered in the future is which combination of drugs interfering with the RAAS will achieve the most beneficial effects. Finally, the VALUE trial reminds us that, alongside the favorable effects of RAAS blockade, which exceed the effect of blood pressure lowering alone, strict blood pressure control is the most important issue of antihypertensive therapy.

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