Regression of Left Ventricular Mass by Antihypertensive Treatment
A Meta-Analysis of Randomized Comparative Studies

Robert H. Fagard, Hilde Celis, Lutgarde Thijs, Stijn Wouters

Abstract—Blood pressure–lowering therapy reduces left ventricular mass, but the question of whether differences exist among drug classes has not been fully resolved. Our aim was to compare the effects of diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers on left ventricular mass regression in patients with hypertension on the basis of prospective, randomized comparative studies. We performed meta-analyses, involving pooled pairwise comparisons of the drug classes and of each class versus other classes statistically combined, and meta-regression analyses to identify the determinants of the regression. The 75 relevant publications involved 84 pairwise comparisons and 6001 patients. Regression of left ventricular mass was significantly less (P=0.01) with β-blockers (9.8%) than with angiotensin receptor blockers (12.5%), but none of the other analyzable pairwise comparisons between drug classes revealed significant differences (P>0.10). In addition, β-blockers showed less regression than the other 4 classes statistically combined (P<0.01), and regression was more pronounced with angiotensin receptor blockers versus the others (P<0.01). In multivariable meta-regression analysis on all of the treatment arms, β-blocker treatment was a significant and negative predictor of the regression (−3.6%; P<0.01), but this was not the case for the other drug classes, including angiotensin receptor blockers. In conclusion, β-blockers show less regression of left ventricular mass, whereas angiotensin receptor blockers may induce larger regression. The inferiority of β-blockers appears to be more convincing than the superiority of angiotensin receptor blockers. (Hypertension. 2009;54:00-00.)

Key Words: angiotensin-converting enzyme inhibitor ■ angiotensin receptor blocker ■ β-blocker ■ calcium channel blocker ■ diuretic ■ left ventricular mass ■ meta-analysis

There is little doubt that blood pressure (BP)–lowering therapy reduces left ventricular (LV) mass (LVM) in patients with hypertension in comparison with placebo treatment.1-3 However, the question of whether differences exist among drug classes remains a matter of debate. Meta-analyses have suggested that angiotensin-converting enzyme (ACE) inhibitors might be more effective than other first-line therapies1,2; that ACE inhibitors and, to a lesser extent, calcium channel blockers, rather than diuretics and β-blockers, emerge as first-line candidates to reduce LVM;4 and, more recently, that angiotensin receptor blockers also favorably reduce LVM.4 Advantages of the meta-analytic technique are the increased statistical power and the more accurate estimate of the magnitude of the effect,5 but the results largely depend on the criteria for the inclusion of studies. In early meta-analyses on the regression of LVM, the majority of the included studies were open, uncontrolled, single-drug studies, which may seriously hamper their interpretation.1,2 A subsequent meta-analysis5 only included studies that compared different drug classes in randomized designs, but this meta-analysis was criticized, because the results were reported separately for the different drug classes, without respect for the original pairwise design.6 An earlier meta-analysis of prospective, comparative, randomized studies in which ≥2 classes of drugs were compared, including diuretics, β-blockers, calcium channel blockers, and ACE inhibitors, found no differences in the regression of LVM in pairwise comparisons of each class versus the other 3 classes statistically combined.7 However, the number of eligible studies was small at that time, limiting pairwise comparisons between 2 drug classes,7 but has since considerably increased and now also includes studies involving angiotensin receptor blockers. The aim of the current meta-analysis was to perform, in patients with hypertension, pooled pairwise comparisons of the effects of the 5 major drug classes on LVM regression, to perform pooled pairwise comparisons of each drug class versus other classes statistically combined, and to identify the determinants of the regression of LVM by the use of multivariable meta-regression analysis.
Methods

Selection of Studies

Our database of prospective, randomized comparative studies on the effects of different antihypertensive drug classes on echocardiographic LVM was initiated in the early 1990s,\(^7\) updated in 2001,\(^4\) and again updated in 2007 to April 2009 for the current meta-analysis. We conducted a comprehensive literature search with the Medline and PubMed computerized databases for studies from the first publication up to December 2008, with the following medical subject headings: LVM; LV hypertrophy (LVH); regression; and each class of antihypertensive drugs; for the angiotensin receptor blockers we also performed searches for each drug separately. The reference lists of the original articles and reviews on the topic were examined to identify other eligible studies. Selection criteria for inclusion in the meta-analysis were as follows: comparison of the effect of antihypertensive drugs, belonging to different drug classes (diuretics, \(\beta\)-blockers, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers), on echocardiographic LVM or LVM index (hereby indicated as LVM); parallel group design with random allocation to treatment arms; involving adult hypertensive patients without cardiovascular or renal disease or other clinical conditions, such as diabetes; initiation of drug treatment with monotherapy, with or without add-on therapy for better BP control, provided it was the same in all of the treatment arms; no other interventions or treatment, with interruption of all BP-lowering drugs before the run-in period; availability of echocardiographic LVM in \(\geq 70\%\) of patients in \(\geq 1\) visit after randomization (in case of multiple examinations, the last visit with \(\geq 70\%\) of analyzable data was taken); treatment duration of \(\geq 2\) months; reporting of LVM at baseline and during treatment or at baseline with changes from baseline; availability of baseline data and follow-up data in each treatment arm; and full publication in a peer-reviewed journal up to December 2008, with the exclusion of data repeats.

Data Extraction

We used a standardized data extraction form for collecting the following data: name of the first author and year of publication; study design; treatment regimens; sample size; patient characteristics; LVM; and, if available, LV internal dimension, wall thickness, fractional shortening, ejection fraction, LV inflow characteristics (ratio of early to late diastolic filling) from Doppler echocardiography, and BP and heart rate. The data were extracted by 1 reviewer and checked by an independent reviewer; disagreements were resolved by discussion.

Statistical Analysis

Statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc). Descriptive data of treatment groups and participants are given as the mean or median and range. The treatment-induced change in LVM was the primary endpoint of the current meta-analysis. We calculated the change in LVM within each treatment arm of each study as the percentage of change in LVM or in the LVM index when only the latter was available on the basis of the reported mean data or change. Because of methodologic differences among studies, changes in BP and other variables are also expressed as percentage changes. We also calculated the slope of the percentage change in LVM on the percentage change in systolic BP (hereby called the \("dLVM/dSBP slope\). Changes within treatment arms are reported as mean±SEM, weighted for the number of analyzable participants. In the primary analysis, we performed separate meta-analyses of each pairwise comparison of 2 drug classes, respecting the comparative design of the original studies, and weighting for the number of analyzable participants. For each comparison, we report the pooled difference of the percentage change of the newer drug class minus the percentage change of the older drug class as weighted mean±SEM. The fixed-effects model was used as the default method to estimate the differences among drug classes; we used the random-effects model in case of significant statistical heterogeneity, which was assessed by \(\chi^2\) tests. In secondary analyses, we performed meta-analyses of the pairwise comparisons of each drug class with other classes statistically combined. Furthermore, we performed exploratory analyses on other variables (ie, LV internal diameter, wall thickness, and indices of systolic and diastolic LV function) without an attempt to statistically compare drug classes because of the smaller number of available data. Finally, we performed multi-variable weighted meta-regression analyses using all of the treatment arms to identify the determinants of the regression of LVM, in which each of the 5 drug classes was offered as a dummy variable, together with a number of covariates with a potential effect on LVM regression. A 2-sided \(P\leq0.05\) was considered significant.

Results

Overview of Trials

We identified 75 publications that fulfilled the selection criteria.\(^5\)–\(^83\) Two articles reported, respectively, 2 and 3 separate randomized studies, and 3 studies included 3 treatment arms, so that the number of studies amounted to 78, and the number of randomized pairwise comparisons amounted to 84. Sample size of the studies ranged from 16 to 960 participants (median: 40 participants), totaling 6001 participants. Dropout varied from 0.0% to 30.0% (median: 5.7%). Average age ranged from 38.0 to 79.0 years (mean: 53.8 years) and the percentage of men from 21.0% to 100.0% (mean: 63.1%). All of the patients had hypertension by definition, and 43.6% of the studies required the presence of LVH. A total of 76.4% of the studies included patients on antihypertensive treatment, which was interrupted for variable periods of time during the run-in period before randomization. The study design was double-blind in 60.3% of the studies and single-blind with blinded echocardiographic assessment in 25.6%, and this information was not given in the remaining 14.1%. Drug treatment consisted of monotherapy in 59.0% of the studies, whereas 41.0% allowed add-on therapy. Median study duration was 6 months (range: 2 to 48 months). Table 1 summarizes the numbers of pairwise comparisons, with information on study design and the total number of participants involved in each comparison. Altogether, diuretics, \(\beta\)-blockers, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers were involved in, respectively, 24, 31, 44, 49, and 20 comparisons. The most frequently used diuretics were hydrochlorothiazide (n=11), indapamide (n=6), and chlorothalidone (n=3). Twenty-three of the 31 studies with \(\beta\)-blockers involved cardioselective drugs (20 with atenolol), 6 nonselective drugs, and 2 drugs with ancillary properties (1 with carvedilol and 1 with nebivolol). Only 7 of the 44 studies with calcium channel blockers were performed with nondihydropyridine drugs (ie, 4 with verapamil, 2 with diltiazem, and 1 with mibefradil; nifedipine and amlodipine were used in 14 and 8 comparisons, respectively). The most frequently used ACE inhibitors were enalapril (n=15), lisinopril (n=10), perindopril (n=6), and fosinopril (n=4), and the most frequently used angiotensin receptor blockers were losartan (n=6), telmisartan (n=4), and valsartan (n=4).

Overall Results

LVM was reduced by 10.3±0.88% (P<0.001) from a baseline value of 248±4.4 g (n=66) and LVM index by 11.0±0.60% (P<0.001) from a baseline value of 132±1.6 g/m\(^2\) (n=140). The overall LVM reduction in the 168
Changes in LV internal diameter and wall thickness were reported in 84 and 96 treatment groups, respectively. The internal diameter decreased by 0.64 ± 0.53% (P < 0.01) from an initial value of 50.7 ± 0.29 mm and total wall thickness (the sum of septal and posterior wall thicknesses) by 6.2 ± 0.53% (P < 0.001) from a baseline value of 23.0 ± 0.23 mm. Fractional shortening and ejection fraction increased by, respectively, 7.00 ± 1.71% (n = 44; P < 0.001) and 3.30 ± 1.08% (n = 42; P < 0.01) from baseline values of 34.49 ± 1.04% and 65.09 ± 0.88%. Overall LV systolic function (fractional shortening or, if not reported, ejection fraction) increased by 5.80 ± 1.22% (n = 66; P < 0.001). The ratio of early to late diastolic filling averaged 0.92 ± 0.02 at baseline and increased by 8.9 ± 2.2% (n = 52; P < 0.001). BP averaged 165.30 ± 22.70 mm Hg at baseline and decreased by 13.50 ± 0.29% for systolic BP (n = 156; P < 0.001) and by 13.50 ± 0.26% for diastolic BP (n = 164; P < 0.001). The dLVM/dSBP slope averaged 0.83 ± 0.48.

**Pairwise Interclass Comparisons Among 5 Drug Classes**

Six or more studies are available for 8 of the 10 possible interclass pairwise comparisons (Table 1). The figure shows the summary statistics of the respective differences of the percentage changes in LVM and systolic BP with the newer drug class minus the percentage changes in LVM and BP with the older drug class. We observed no significant interclass differences for the regression of LVM, except for the comparison of β-blockers with angiotensin receptor blockers. β-Blockers reduced LVM by 9.8 ± 2.0%, whereas the reduction amounted to 12.5 ± 2.6% with angiotensin receptor blockers (P = 0.01). In addition, heart rate (reported for 6 of the 9 comparisons) was reduced by 11.90 ± 0.91% with β-blockers and by 2.40 ± 0.64% with angiotensin receptor blockers (P < 0.001). In none of the pairwise comparisons were the reductions in systolic BP (Figure) and diastolic BP (data not shown) significantly different between 2 drug classes. The difference in regression of LVM between β-blockers and angiotensin receptor blockers remained significant for the dLVM/dSBP slope, that is, 0.64 ± 0.14 for β-blockers and 0.76 ± 0.17 for angiotensin receptor blockers (P < 0.05). The figure also shows data from the individual studies when only 2 comparisons were available (i.e., angiotensin receptor blockers versus, respectively, diuretics and calcium channel blockers). It is noteworthy that the reduction of LVM appears to be more pronounced with the angiotensin receptor blocker in these studies, but differences in BP have to be considered.

**Pairwise Comparison of Each Drug Class With Other Classes Statistically Combined**

As shown in Table 2 the regression of LVM with, respectively, diuretics, calcium channel blockers, or ACE inhibitors was not significantly different from the regression observed with the other 4 classes statistically combined (P > 0.30). However, regression was worse with β-blockers (P = 0.002) and better with angiotensin receptor blockers (P = 0.002). These findings persisted for the dLVM/dSBP slope. The slope amounted to 0.63 ± 0.09 for β-blockers and 0.81 ± 0.10 for the others (P = 0.02) and to 0.85 ± 0.12 for angiotensin receptor blockers and 0.65 ± 0.09 for the others (P = 0.05).

After exclusion of the comparisons with angiotensin receptor blockers from the analysis, the reduction in LVM amounted to 7.50 ± 1.16% with β-blockers and to 10.00% ± 1.20% with the 3 other classes statistically combined (P = 0.10; 22 comparisons, including 1000 patients); the slopes averaged, respectively, 0.65 ± 0.13 with β-blockers and 0.88 ± 0.12% with the others (P = 0.09). After exclusion of β-blockers, the reduction in LVM averaged 12.70 ± 1.47% with angiotensin receptor blockers and 8.70 ± 1.78% with the 3 other classes (P = 0.06; 9 comparisons with 704 patients), with slopes of, respectively, 1.04 ± 0.18 and 0.69 ± 0.12 (P = 0.14).

<table>
<thead>
<tr>
<th>Drug Classes</th>
<th>Comparisons</th>
<th>No.</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIU BB</td>
<td>All</td>
<td>62</td>
<td>9,21,22,26,28,66</td>
</tr>
<tr>
<td>DIU CCB</td>
<td>DB</td>
<td>9</td>
<td>9,10,17,21,28,32,38,57,66</td>
</tr>
<tr>
<td>DIU ACEi</td>
<td>PROBE LVH+</td>
<td>7</td>
<td>15,20,25,28,40,50,54</td>
</tr>
<tr>
<td>BB CCB</td>
<td>Mono</td>
<td>2</td>
<td>51,72</td>
</tr>
<tr>
<td>BB ACEi</td>
<td></td>
<td>9</td>
<td>9,12,16,21,48,66,76</td>
</tr>
<tr>
<td>BB ARB</td>
<td></td>
<td>9</td>
<td>13,14,24,27,31,33,55,60,70</td>
</tr>
<tr>
<td>CCB ACEi</td>
<td></td>
<td>9</td>
<td>35,52,59,65,71,73,79,80,83</td>
</tr>
<tr>
<td>CCB ARB</td>
<td></td>
<td>2</td>
<td>42,6,48,9,10,12,16,21,28,32,38,57,66</td>
</tr>
<tr>
<td>ACEi ARB</td>
<td></td>
<td>2</td>
<td>53,56,63,64,74,77,81</td>
</tr>
</tbody>
</table>

ACEi indicates ACE inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; DB, double-blind; DIU, diuretic; LVH+, selected for LVH; Mono, monotherapy, without add-on treatment; PROBE, prospective open with blind endpoint evaluation.

### Table 1. Number of Pairwise Comparisons of 2 Drug Classes and Number of Patients in Each Comparison

<table>
<thead>
<tr>
<th>Drug Classes</th>
<th>Comparisons</th>
<th>Older</th>
<th>Newer</th>
<th>All</th>
<th>DB</th>
<th>PROBE</th>
<th>LVH+</th>
<th>Mono</th>
<th>Patients</th>
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</thead>
<tbody>
<tr>
<td>DIU BB</td>
<td></td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>285</td>
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<td>9,21,22,26,28,66</td>
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<tr>
<td>DIU CCB</td>
<td></td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>322</td>
<td></td>
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<tr>
<td>DIU ACEi</td>
<td></td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>597</td>
<td></td>
<td>15,20,25,28,40,50,54</td>
</tr>
<tr>
<td>BB CCB</td>
<td></td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>135</td>
<td></td>
<td>51,72</td>
</tr>
<tr>
<td>BB ACEi</td>
<td></td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>291</td>
<td></td>
<td>13,14,24,27,31,33,55,60,70</td>
</tr>
<tr>
<td>BB ARB</td>
<td></td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1680</td>
<td></td>
<td>35,52,59,65,71,73,79,80,83</td>
</tr>
<tr>
<td>CCB ACEi</td>
<td></td>
<td>26</td>
<td>9</td>
<td>10</td>
<td>14</td>
<td>17</td>
<td>1211</td>
<td></td>
<td>11,18,19,23,29,30,34,36,37,39,41,47,49,58,61,62,68,69,78,82</td>
</tr>
<tr>
<td>CCB ARB</td>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>143</td>
<td></td>
<td>67,75</td>
</tr>
<tr>
<td>ACEi ARB</td>
<td></td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>426</td>
<td></td>
<td>53,56,63,64,74,77,81</td>
</tr>
</tbody>
</table>
Mechanisms of LVM Regression

Wall thickness was significantly reduced by each class of drugs: diuretics (−3.40±0.60%; n=16); β-blockers (−4.10±0.92%; n=18); calcium channel blockers (−9.30±0.85%; n=24); ACE inhibitors (−7.40±1.12%; n=28); and angiotensin receptor blockers (−5.30±1.92%; n=10; P<0.001 for all, except P<0.05 for angiotensin receptor blockers). LV internal dimension was significantly reduced by diuretics (−2.00±0.66%; P<0.01) and, to a smaller extent, by angiotensin receptor blockers (−0.71±0.27%; P<0.05) but not by the other drugs (P>0.10). Relative wall thickness was reduced by all of the drug classes (P<0.01), except diuretics (P=0.27).

Determinants of LVM Regression

Table 3 gives the results of the multivariable meta-regression analysis, weighted for the number of analyzable participants in each treatment arm, to identify the determinants of the percentage of reduction in LVM. Regression of LVM was more pronounced when study duration was longer; when LVH was a selection criterion for inclusion in the study; and with larger reductions in systolic BP. Regression was less in the double-blind studies and in studies that included patients with previous antihypertensive treatment but was not influenced by age and plasma half-life of the individual drugs. Finally, among the 5 drug classes, only β-blockers entered the model with a 3.6% lesser reduction of LVM (P<0.01). Changes in LVM were not significantly related to changes in heart rate, which were, however, reported in only 63 treatment arms (13 on β-blockers).

Discussion

The main results of the current meta-analysis of randomized trials in which the effects of the 5 major antihypertensive drug classes on the regression of echocardiographic LVM or LVM index are directly compared are described here. First, in pairwise comparisons of the 5 drug classes, the only significant difference between drug classes is a lesser regression in LVM by β-blockers than by angiotensin receptor blockers.

![Figure](http://hyper.ahajournals.org/.../H11022)

Figure. Pairwise comparisons of 5 drug classes. Data are pooled differences±SEM between the percentage change of LVM (index) (left) or systolic BP (right) with the newer drug class and the percentage change of LVM (index) or systolic BP with the older drug class (full lines). The results of individual studies are given in cases of only 2 available comparisons (broken lines). A negative value in the direction of the arrow means that the regression is more pronounced with the newer drug class in comparison with the older drug class, and a positive value means that the regression is less pronounced with the newer drug class. The P value indicates the statistical significance; NS, not significant (P>0.05).

Table 2. Pairwise Comparison of Each Drug Class With the Other Classes Statistically Combined

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>N</th>
<th>n</th>
<th>Reference Drug</th>
<th>Other Drugs</th>
<th>P</th>
<th>Change in LVM (Index), %</th>
<th>N</th>
<th>n</th>
<th>Reference Drug</th>
<th>Other Drugs</th>
<th>P</th>
<th>Change in Systolic BP, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIU</td>
<td>24</td>
<td>1339</td>
<td>−7.6±1.18</td>
<td>−8.3±1.80</td>
<td>NS</td>
<td>21</td>
<td>1251</td>
<td>−11.9±0.73</td>
<td>−12.6±0.87</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB</td>
<td>31</td>
<td>2680</td>
<td>−8.8±1.05</td>
<td>−11.6±1.23</td>
<td>0.002</td>
<td>29</td>
<td>2634</td>
<td>−13.8±0.67</td>
<td>−14.0±0.67</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>CCB</td>
<td>44</td>
<td>2100</td>
<td>−12.8±0.06</td>
<td>−13.6±1.00</td>
<td>NS</td>
<td>41</td>
<td>1995</td>
<td>−12.2±0.56</td>
<td>−12.4±0.56</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi</td>
<td>49</td>
<td>2525</td>
<td>−11.4±1.18</td>
<td>−10.4±1.00</td>
<td>NS</td>
<td>45</td>
<td>2426</td>
<td>−13.6±0.51</td>
<td>−13.7±0.49</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>20</td>
<td>2384</td>
<td>−12.6±1.50</td>
<td>−9.4±1.33</td>
<td>0.002</td>
<td>20</td>
<td>2384</td>
<td>−14.9±0.83</td>
<td>−14.0±0.83</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are weighted mean±SEM. ACEi indicates ACE inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; DIU, diuretic; n, No. of participants; N, No. of pairwise comparisons; NS, not significant (P>0.3 for all comparisons).
Table 3. Determinants of the Percentage of Reduction of LVM (Index) in Weighted Stepwise Multivariable Metaregression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial Regression Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>(+10.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study duration, mo</td>
<td>+0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVM at baseline*</td>
<td>+2.15</td>
<td>0.05</td>
</tr>
<tr>
<td>Systolic BP reduction, %</td>
<td>+0.26</td>
<td>0.05</td>
</tr>
<tr>
<td>Previous antihypertensive treatment*</td>
<td>-4.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Double-blind design*</td>
<td>-4.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-blockers*</td>
<td>-3.63</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>R²</td>
<td>0.33</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

No. of treatment arms without lacking data: 154. Data are partial regression coefficients, except for the intercept, and P values for statistical significance. Age, other drug classes, and plasma half-life of individual drugs did not enter the model (P=0.15).

*Data were coded as yes=1 and no=0.

Second, in pairwise comparisons of each drug class with the other classes statistically combined, β-blockers show less regression of LVM, and angiotensin receptor blockers show more pronounced regression. Third, regression of LVM is based on a reduction of wall thickness by all of the drug classes and an additional relevant reduction of the internal diameter by diuretics. Fourth, in multivariable meta-regression analysis on all of the treatment arms, only β-blockers have an independent and negative effect on LVM regression.

Our results are at variance with previous meta-analyses. The earliest meta-analyses1,2 concluded that ACE inhibitors are more effective than other first-line therapies, that is, diuretics, β-blockers, and calcium channel blockers. However, all of the available studies were included in these meta-analyses, and the majority of the studies were open and uncontrolled, which limits the validity of the results. By contrast, in a subsequent meta-analysis of randomized, active comparisons only, the reduction of LVM by, respectively, diuretics, β-blockers, calcium channel blockers, and ACE inhibitors appeared to be similar to the reduction obtained with the other 3 classes statistically combined, and the pairwise comparison of the 4 studies that directly compared ACE inhibitors with calcium channel blockers showed almost identical reductions in LVM.3 However, the number of available randomized active comparison studies was limited at that time. Schmieder et al1 performed a meta-analysis of all of the published articles, including only double-blind, randomized, controlled studies with parallel-group design. They concluded that ACE inhibitors reduce LVM more than β-blockers and diuretics, with calcium channel blockers somewhat in the intermediate range. However, this meta-analysis was criticized because each treatment arm of the double-blind, randomized, controlled clinical trials was taken as a separate observation without respect for the original comparative design.6 In a more recent meta-analysis of 5 drug classes,4 the same group reported that, when each treatment arm was taken as a separate observation, there were significant differences in the reduction of LVM among the 5 drug classes (P=0.004). LVM decreased by 13% with angiotensin receptor blockers, by 11% with calcium channel blockers, by 10% with ACE inhibitors, by 8% with diuretics, and by 6% with β-blockers. In the same report, the authors also performed pairwise comparisons between drug classes and found that angiotensin receptor blockers, ACE inhibitors, and calcium channel blockers reduced LVM significantly more than did β-blockers. However, the statistical methodology of the latter secondary analysis was not described in detail, and diuretics were not included in the pairwise comparisons.7 It is noteworthy that, if we had only performed separate analyses of each drug class, we would have concluded that regression of LVM would not only be less with β-blockers but also with diuretics, but this was not confirmed in the proper pairwise analyses.

In contrast with previous meta-analyses, we only observed a significant difference between angiotensin receptor blockers and β-blockers in the pairwise comparisons of 2 drug classes, and this difference was maintained when the BP changes were taken into account. The LVM regression with β-blockers was, on average, 23% less than with angiotensin receptor blockers if expressed in percentage of the 12.5% reduction obtained with angiotensin receptor blockers. In addition, β-blockers tended to be less effective than diuretics, calcium channel blockers, and ACE inhibitors in the separate pairwise comparisons. When the overall pairwise comparison was repeated with the exclusion of angiotensin receptor blockers, the difference between β-blockers and the 3 other classes was of the same magnitude as the difference between β-blockers and angiotensin receptor blockers, although short of statistical significance, in which the smaller sample size should be taken into account. Finally, in the meta-regression analysis of all of the treatment arms, which we performed to define the determinants of the regression of LVM, β-blockers showed an independent negative effect, which amounted to 3.6%. One plausible explanation for the lesser regression of LVM by β-blockers is that central aortic pressure is reduced less than brachial artery pressure, so that afterload reduction is less with β-blockers than with the other drugs.84 Also, the lower heart rate could play a role, but the reduction in LVM was not related to the change in heart rate in the treatment arms in which it was reported. It is noteworthy that 20 of the 31 paired comparisons were performed with atenolol and the 8 other comparisons with a variety of other β-blockers. Nevertheless, the test of heterogeneity was not significant, suggesting that the results of the individual studies are compatible with the overall result. However, it cannot be excluded that the results would be more favorable with third-generation β-blockers with potentially beneficial ancillary properties, but we identified only 1 comparative study with nebivolol79 and 1 with carvedilol.80

In the overall analysis, the regression of LVM by angiotensin receptor blockers is significantly better than with the other drugs statistically combined. Even after the exclusion of β-blockers and comparison with the other 3 classes, the difference in favor of angiotensin receptor blockers is close to statistical significance (P=0.06) and amounts to 4%, although part of the difference may be related to better BP control. However, in the multivariable meta-regression analysis on the determinants of the regression of LVM, angiotensin...
sin receptor blockers are far from significant when forced in the equation \( P>0.68 \), so that other factors seem to play a role in the better regression by these drugs. Altogether, the superiority of angiotensin receptor blockers with regard to LVM regression appears to be less convincing than the inferiority of \( \beta \)-blockers. The effect on the renin-angiotensin system is often invoked to explain the possible superiority of BP-lowering drugs, which interfere with this system, but it is of note that the regression of LVM is not significantly different in the pairwise comparison of calcium channel blockers and ACE inhibitors. On the other hand, drugs that act on the renin-angiotensin system appear to have similar effects on the regression of LVM, as shown by the almost identical regression by angiotensin receptor blockers and ACE inhibitors and by the recent report that the direct renin inhibitor aliskiren is as effective as losartan in promoting LVM regression.\(^{85}\)

We also extracted data on LV systolic and diastolic functions, but because of the paucity of data, we have not analyzed the effects of the different drug classes. However, it is of interest that the LV fractional shortening and ejection fraction as indices of systolic function and the LV inflow ratio of early to late diastolic filling as an index of diastolic function all improved in response to antihypertensive treatment. However, these results should be interpreted with caution, because they are not controlled.

Results from meta-analyses have to be interpreted with some caution, but, although meta-analyses are no substitute for large, well-designed trials, the meta-analytic technique is probably the best method to systematically review previous work.\(^{5}\) Advantages are the greater precision of the estimates and the enhanced statistical power. Potential disadvantages are publication bias and the heterogeneity of studies. Although heterogeneity can be addressed by applying the random-effects model, it is, unfortunately, not possible to identify all of the relevant unpublished material.

**Perspectives**

It is well known that more pronounced regression of electrocardiographic\(^{86}\) or echocardiographic\(^{87}\) LVM during antihypertensive treatment is independently associated with a better prognosis so that different effects of blood-lowering drugs on LVM may be clinically relevant. Meta-analyses suggest that \( \beta \)-blockers are less protective for cardiovascular events than other drug classes,\(^{88,89}\) but, as in the studies of LVM regression, most trials were conducted with atenolol as first-line treatment. Studies are needed to assess the association of the lesser regression of LVM by \( \beta \)-blockers and the presumed smaller impact on prognosis and to investigate LVM regression and outcome with other \( \beta \)-blockers, particularly those with potentially favorable ancillary properties. Finally, more studies are needed with angiotensin receptor blockers to find out if they do indeed reduce LVM to a greater extent than other antihypertensive agents and if this effect would lead to a better prognosis.

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**Disclosures**

None.

**References**


8. Fagard RH. A meta-analysis on comparative studies on left ventricular mass regression. Presented at the 23rd Congress of the European Society of Cardiology; September 1–5, 2001; Stockholm, Sweden.


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