Studies on Left Ventricular Hypertrophy Regression in Arterial Hypertension: A Clear Message for the Clinician?

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BACKGROUND
Evidence-based medicine should provide clear and unbiased information to clinicians. We conducted an analysis on published randomized trials evaluating the effects of antihypertensive therapy on left ventricular (LV) morphology assessed by echocardiography to investigate (i) the consistency of criteria used for definition of LV hypertrophy (LVH) and (ii) the consistency of the way LVH regression and blood pressure (BP) control were reported.

METHODS
Studies identified by a PubMed search were eligible for inclusion in the analysis, if they fulfilled the following criteria: (i) publication in a peer-reviewed journal within the last 12 years; (ii) double blind, randomized, controlled, parallel-group design; (iii) numerosity of at least 50 adult hypertensive subjects; (iv) follow-up duration of at least 6 months; (v) comparison between single-drugs or association regimens; (vi) LV mass (LVM) or wall thickness measured by echocardiography.

RESULTS
Thirty-nine trials, including 9,162 hypertensive subjects of both genders in 78 active treatment arms or in 6 placebo arms were identified. Definition of LVH was provided by 34 studies (87.1%) according to 19 different criteria. All trials evaluated LVH regression as the absolute or relative changes of continuous variables such as LVM index (LVMI) or LV wall thickness. Data concerning prevalence rates of LVM normalization were reported in 12 studies (30.7%). The percentage of patients reaching BP target (<140/90 mm Hg) was reported in 11 studies (28.2%).

CONCLUSIONS
Our findings indicate that (i) definition of hypertensive LVH phenotype is extremely variable, and (ii) no precise information on LVH regression rates or changes in LV geometrical patterns, as well as on target BP, is provided by the majority of papers.


Left ventricular hypertrophy (LVH) assessed by standard echocardiography represents a strong, independent predictor of increased cardiovascular (CV) morbidity and mortality in a variety of settings.1–3 In hypertensive patients, LVH is clinically relevant because it represents an integrated marker of CV risk and reflects the long-term effects on the heart of hemodynamic and nonhemodynamic factors operating in hypertension. Thus, detection of LVH in hypertensive patients who would be classified as at low or moderate CV risk, if assessed by routine procedures, including an electrocardiogram, is crucial for stratifying total CV risk and for grading the therapeutic approach according to absolute risk.4–6

A large body of evidence indicates that LVH may be reversed by nonpharmacological and pharmacological interventions. Prospective studies in hypertensive cohorts7–9 and in a general population sample10 have shown that regression of LVH is associated with reduced CV complications. Overall, these findings support the view that the value of LV mass (LVM) and its reduction during chronic antihypertensive treatment may provide relevant information on CV disease and direct therapeutic decisions.7,11

Several hundred echocardiographic studies have tested the effects of antihypertensive drugs on LVH regression and have provided useful indications for the management of patients with cardiac hypertrophy. However, as outlined by guidelines,6 many studies did not follow strict scientific criteria in their methodological design, particularly as far as randomization, sample size, and analytic criteria aimed at minimizing regression to the mean and reader’s bias, thus leading to potential unreliability. Additional limitations are represented by differences in criteria for LVH definition used by insufficient or absent information about important clinical points such as the rates of normalization of LVM and blood pressure (BP); changes in LV geometry, and for comparative randomized trials the real equivalence of BP changes. Thus, we undertook an analysis of LVH regression studies published in the last 12 years to answer the following question: How many of the published trials have provided sufficiently detailed data so that useful information can be
drawn for medical practice? To this purpose, we have investigated consistency in (i) the use of criteria to define LVH; and (ii) in reporting data about LVH regression, LV geometrical patterns, and BP changes.

METHODS

Studies were eligible for inclusion in the analysis, if they fulfilled the following predefined criteria: (i) publication in a peer-reviewed journal, (ii) randomized, double blind, active treatment, or placebo-controlled with parallel-group design; (iii) at least a total of 50 adult subjects (age ≥ 18 years) with clinical diagnosis of hypertension according to current standard criteria; (iv) follow-up duration of at least 6 months; (v) comparison between single-drugs or association regimens (i.e., two or more drugs); (vi) LVM or wall thickness measured by echocardiography.

Studies have been identified by a PubMed search with headings “hypertension,” “left ventricular hypertrophy,” “regression,” and “echocardiography.” Only full articles published in English language from January 1, 1995 to December 31, 2006 were included. Data were extracted by three independent investigators (A.E., F.N., and M.M.).

The initial search identified 119 trials, of which 39 only fulfilled the inclusion criteria (Figure 1). These are consecutively listed in the reference section according to the date of publication.12–50

RESULTS

Characteristics of the studies

The 39 trials included 9,162 hypertensive subjects of both genders in 78 active treatment arms or 6 placebo arms (Tables 1 and 2). Angiotensin converting enzyme–inhibitors (26 treatment arms), followed by calcium-antagonists (18), angiotensin receptor antagonists (15), β-blockers (13), and diuretics (10) were the most frequently investigated antihypertensive agents. Duration of treatment ranged from 24 to 260 weeks; and in more than half of the studies it was of at least 48 weeks. Twenty-four studies (61.5%) were multicenter national or international trials; and reading of echocardiographic scans was performed in centralized core laboratories, except in two studies.25,29 Twenty-seven out of thirty-nine studies were sponsored by industry (12 different companies), while two other studies were endorsed or received financial support by scientific societies.

Characteristics of the subjects

A common feature of the studies was the population study, mostly represented by selected uncomplicated hypertensive subjects with preserved LV systolic function, without valvular heart disease, cardiomyopathy, and underlying coronary heart disease. Two studies were carried out in hypertensive subjects with type 2 diabetes mellitus19,23 and three further studies in the setting of chronic renal failure18 or renal transplantation, respectively.27,30 Age ranged from 18 to 80 years, but detailed information on the age range was provided by 28 studies only.12,14,17–21,23–43,45,46,48 All but one included subjects of both genders; male gender was prevalent, with a male/female ratio of 1.89. Presence of LVH was a prespecified inclusion criterion in only 14 of the 39 studies (35.9%); subjects were included independently of their baseline LVM level in 8 trials (20.5%), while no information was provided on this point by the remaining 15 (38.4%).

Criteria for LVH, hypertrophy regression, and BP control

Definition of echocardiographic LVH was provided by 34 studies (87.1%), according to 19 different criteria, with all but one based on LVM indexed (LVMI) mostly to body surface area, more rarely to height or height.2,7 Gender-specific partition values and indexation of LVM to body surface were used in the large majority of trials (85 and 95%, respectively). A few trials provided more than one LVH definition (i.e., age-related thresholds). LVMI ≥134 g/m² in men and 110 g/m² in women was the prevalent LVH diagnostic criteria, followed in ranking order by 130/110 g/m² and 120/100 g/m². A gender-based analysis revealed that definition of LVH in women was mostly based on the partition value of 110 g/m² (14 out of 35 studies); this was the case for the cutoff of 134 g/m² in men (10 studies). Partition values in men ranged from 116 g/m² to 143 g/m², in women from 98 g/m² to 110 g/m².

Information on LV geometry at baseline (i.e., eccentric or concentric LVH and LV concentric remodeling) was provided by only five studies.14,33,34,36,49

Prevalence of LVH regression and BP control

All trials evaluated LVH regression as the absolute or relative changes of the continuous variable LVM and LVMI. The prevalence rates of the subjects with normalized LVM (defined as mass below the cutoff used for LVH) were reported in 12 studies, and information about the changes in geometrical LV patterns was available in approximately half of them. Incidence of full LVH regression ranged between 10 and 100%.

Baseline and on-treatment mean clinic BP values were indicated in almost all studies; however, only 11 of them (27.5%)
reported the prevalence rates of BP normalization according to the target value recommended for the hypertensive population (clinic BP <140/90 mm Hg) by major hypertension guidelines.

**DISCUSSION**

The present analysis of 39 studies focusing on regression of cardiac hypertrophy in human hypertension published in the last decade provides important insights: (i) LVH was variably defined according to as many as 19 different echocardiographic criteria; (ii) information on fundamental therapeutic targets such as the rates of LVM and BP normalization or changes in LV geometrical patterns was provided by a minority of these trials.

The following aspects of our findings deserve to be discussed.

First, it has been frequently pointed out that studies on LVH regression induced by antihypertensive treatment should be based on rigorous methodological criteria: randomized double blind design, technical features minimizing regression to the mean and readers’ bias, minimum study duration of 9–12 months, and sufficient power (at least 100 patients per arm) to detect relatively small differences between treatment effects. Since a preliminary analysis identified only 11 trials satisfying all the above mentioned criteria, we decided to extend our review to randomized, double blind, active treatment or placebo-controlled trials enrolling at least 50 subjects.

Second, despite the widespread use of quantitative echocardiography over the past 25 years and its indisputable contribution to understanding pathophysiological and clinical aspects of LVH in hypertension, no consistent evidence-based data are available on which cutoff values for defining LVH give the best prediction of CV risk in the hypertensive population. This is because a linear relation exists between LVM and CV risk in individuals with hypertension, and therefore definitions of LVH according any criteria are mostly arbitrary. Furthermore, although several criteria of LVMI for body surface area, height, and height2.7 have been proposed, it is not clear which is the best method of normalization and whether the same method should be used in all clinical settings. For instance, in a large hypertensive cohort at low prevalence of obesity, de Simone et al. have shown that the population risk attributable to LVH was not meaningfully different in relation to

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Randomized studies evaluating the effects of antihypertensive treatment on LV mass</th>
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<tbody>
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<td>Author/ref.</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>Klener et al.12</td>
<td>124</td>
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<tr>
<td>Liebson et al.13</td>
<td>844</td>
</tr>
<tr>
<td>Agabiti-Rosei et al.14</td>
<td>193</td>
</tr>
<tr>
<td>Lièvre et al.15</td>
<td>115</td>
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<tr>
<td>Gottdiener et al.16</td>
<td>1,105a</td>
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<tr>
<td>Papademetriou et al.17</td>
<td>134</td>
</tr>
<tr>
<td>Dyadyk et al.18</td>
<td>72</td>
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<tr>
<td>Scognamiglio et al.19</td>
<td>73</td>
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<tr>
<td>Beltman et al.20</td>
<td>71</td>
</tr>
<tr>
<td>Tedesco et al.21</td>
<td>77</td>
</tr>
<tr>
<td>Thürmann et al.22</td>
<td>69</td>
</tr>
<tr>
<td>Gerritsen et al.23</td>
<td>121</td>
</tr>
<tr>
<td>Höglund et al.24</td>
<td>66</td>
</tr>
<tr>
<td>Sadowski et al.25</td>
<td>76</td>
</tr>
<tr>
<td>Roman et al.26</td>
<td>50</td>
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<tr>
<td>Hernández et al.27</td>
<td>57</td>
</tr>
<tr>
<td>Gosse et al.28</td>
<td>411</td>
</tr>
<tr>
<td>Avanza et al.29</td>
<td>61</td>
</tr>
<tr>
<td>Midtvedt et al.30</td>
<td>154</td>
</tr>
<tr>
<td>Terpstra et al.31</td>
<td>166</td>
</tr>
</tbody>
</table>

HCTZ, hydrochlorothiazide; LV, left ventricular; LVH, LV hypertrophy; NH, nutritional hygienic.

a Only men.
Left Ventricular Hypertrophy Regression Trials

the type of normalization of LVM for body size.51 No specific echocardiographic criteria for LVH detection in hypertensive subjects have been recommended by scientific societies until the year 2003, when the European Society of Hypertension/European Society of Cardiology proposed the partition values of 125 g/m² in men and 110 g/m² in women.6 In 2005, the American Society of Echocardiography/European Association of Echocardiography proposed lower thresholds (i.e., 115 g/m² in men and 95 g/m² in women) derived from multiethnic normal subjects.52 These considerations may partly explain the heterogeneity of echocardiographic criteria used to define LVH in previous studies.

Third, reversal of LVH represents, so far, the most clinically useful intermediate target for assessing the efficacy of antihypertensive treatment. Failure to obtain this target may be related to inadequate therapeutic regimen, noncompliance, true resistant hypertension, or true resistant hypertrophy. Information on LVH regression based on continuous rather than categorical variables (i.e., decrements of LVMI rather than the percentage of patients achieving a cutoff of LVH regression) is certainly useful, but clinical action requires a target to endeavor to achieve. It should be recognized, however, that risk reduction is not necessarily related to complete regression of LVH, but may also rely on a partial reduction of cardiac mass. The Losartan Intervention For Endpoint reduction, one of the largest studies ever done in this research area, showed that losartan-based therapy induced a greater reduction in LVMI from baseline to the last available echocardiogram than atenolol (–21.7 ± 21.8 vs. –17.7 ± 19.6 g/m²).45 How far this apparently small between-treatment difference in LVMI is prognostically important may be difficult to appreciate by practicing physicians if not associated to the report of parallel differences in LVM normalization. Among the studies included in this analysis, only 12 out of 39 studies provided figures about LVM normalization under several antihypertensive regimens, a value ranging from 10 to 100%.

Finally, evaluation of the cardiac hypertensive phenotype should estimate not only LVM but also LV geometry according to validated formulae. Three pathological patterns have been described: concentric hypertrophy (increased LVM and wall-to-radius ratio), eccentric hypertrophy (increased LVM and normal wall-to-radius ratio), and concentric remodeling (normal LVM and increased wall-to-radius ratio). These patterns are associated with different hemodynamic profiles, LV myocardial performances, plasma volumes, clinic and ambulatory BP levels, degrees of body mass index and extracardiac organ damage. Overall, altered LV patterns are associated with

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### Table 2 | Randomized studies evaluating the effects of antihypertensive treatment on LV mass

<table>
<thead>
<tr>
<th>Author/ref.</th>
<th>Number of Subjects</th>
<th>Duration (weeks)</th>
<th>Treatment</th>
<th>LVH criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devereux et al.</td>
<td>303</td>
<td>52</td>
<td>Enalapril vs. nifedipina</td>
<td>Male: &gt;116 g/m², Female: &gt;104 g/m² in women &gt;65 years</td>
</tr>
<tr>
<td>Malmqvist et al.</td>
<td>115</td>
<td>52</td>
<td>Irbesartan vs. atenolol</td>
<td>Male: &gt;131 g/m², Female: &gt;100 g/m²</td>
</tr>
<tr>
<td>Heesen et al.</td>
<td>97</td>
<td>104</td>
<td>Ramipril vs. placebo</td>
<td>Male: &gt;125 g/m²</td>
</tr>
<tr>
<td>Black et al.</td>
<td>171</td>
<td>24</td>
<td>Feliopine vs. placebo</td>
<td>Male: &gt;116 g/m², Female: &gt;104 g/m²</td>
</tr>
<tr>
<td>Cuspidi et al.</td>
<td>196</td>
<td>52</td>
<td>Candesartan vs. enalapril</td>
<td>Male: &gt;120 g/m², Female: &gt;100 g/m²</td>
</tr>
<tr>
<td>De Rosa et al.</td>
<td>50</td>
<td>156</td>
<td>Losartan vs. enalapril</td>
<td>Male: &gt;131 g/m², Female: &gt;100 g/m²</td>
</tr>
<tr>
<td>Dahlof et al.</td>
<td>225</td>
<td>36</td>
<td>Losartan vs. atenolol</td>
<td>Male: &gt;120 g/m², Female: &gt;105 g/m²</td>
</tr>
<tr>
<td>Leenen et al.</td>
<td>217</td>
<td>30</td>
<td>Nifedipine vs. felodipine vs. enalapril vs. placebo</td>
<td>Male: &gt;134 g/m², Female: &gt;110 g/m²</td>
</tr>
<tr>
<td>Gaudio et al.</td>
<td>60</td>
<td>24</td>
<td>Irbesartan vs. amlodipine</td>
<td>Male: &gt;134 g/m², Female: &gt;110 g/m²</td>
</tr>
<tr>
<td>Schneider et al.</td>
<td>240</td>
<td>72</td>
<td>Irbesartan vs. atenolol</td>
<td>Male: &gt;134 g/m², Female: &gt;110 g/m²</td>
</tr>
<tr>
<td>De Luca et al.</td>
<td>214</td>
<td>52</td>
<td>Perindopril/indapamide vs. atenolol</td>
<td>Male: &gt;120 g/m², Female: &gt;100 g/m²</td>
</tr>
<tr>
<td>Libhauser et al.</td>
<td>125</td>
<td>24</td>
<td>Indapamide vs. amlodipine</td>
<td>Male: &gt;134 g/m² and or IVST&gt;12 mm, Female: &gt;110 g/m² and or IVST&gt;12 mm</td>
</tr>
<tr>
<td>Ysunari et al.</td>
<td>66</td>
<td>32</td>
<td>Valsartan vs. amlodipine</td>
<td>Male: &gt;134 g/m² and or IVST&gt;12 mm, Female: &gt;110 g/m² and or IVST&gt;12 mm</td>
</tr>
<tr>
<td>Devereux et al.</td>
<td>960</td>
<td>260</td>
<td>Losartan vs. atenolol</td>
<td>Male: &gt;134 g/m², Female: &gt;110 g/m²</td>
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<tr>
<td>Dahlof et al.</td>
<td>550</td>
<td>52</td>
<td>Perindopril/indapamide vs. enalapril</td>
<td>Male: &gt;120 g/m², Female: &gt;100 g/m²</td>
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<tr>
<td>Agabiti-Rosei et al.</td>
<td>174</td>
<td>208</td>
<td>Lacidipine vs. atenolol</td>
<td>Male: &gt;143 g/m², Female: &gt;102 g/m²</td>
</tr>
<tr>
<td>Galzerano et al.</td>
<td>82</td>
<td>44</td>
<td>Telmisartan vs. carvedilol</td>
<td>Male: &gt;130 g/m², Female: &gt;110 g/m²</td>
</tr>
<tr>
<td>Taniguchi et al.</td>
<td>70</td>
<td>52</td>
<td>Candesartan vs. candesartan + spironolactone</td>
<td>Male: &gt;125 g/m²</td>
</tr>
<tr>
<td>Iaccarino et al.</td>
<td>154</td>
<td>104</td>
<td>Enalapril vs. atenolol</td>
<td>Male: &gt;130 g/m², Female: &gt;110 g/m²</td>
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</table>

IVST, interventricular septum thickness; LVH, left ventricular hypertrophy.
increased rate of CV events, in particular, concentric hyper-
trophy has been consistently proven to be the phenotype at
the highest risk. Again, very few of the studies included
in our analysis described serial variations in LV geometrical
patterns. The Swedish Irbesartan Left Ventricular Hypertrophy
Investigation versus Atenolol study showed that in both
treatment groups ~40% of patients with concentric hyper-
trophy at baseline maintained this LV geometric pattern.33
In the Candesartan Assessment in the Treatment of Cardiac
Hypertrophy study the rates of LVMI normalization were simi-
lar in the candesartan- and enalapril-treated groups (56 vs.
28%); in particular, concentric LVH persisted in 38 and 50%,
respectively, of the candesartan- and enalapril-treated patients
exhibiting concentric LVH at baseline.36
A further important point refers to information about the rates of BP normalization (<140/90 mmHg) provided by these trials.
Although effective BP control plays a pivotal role in promoting
LVH regression, data on this point were provided by only 11
out of 39 studies. As recent large comparative trials (Left ven-
tricular hypertrophy regression: Indapamide Versus Enalapril,
Effects of Amlodipine and Lisinopril on Left Ventricular Mass,
Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement, Candesartan Assessment in the
Treatment of Cardiac Hypertrophy, Losartan Intervention For
Endpoint reduction) showed that target BP was achieved in ~60,
25, 38, 61, and 35% of the patients, respectively, these figures
indicate that effective BP control in patients with LVH represents
a hard target for aggressive therapeutic interventions.28,31,32,36,45
Our analysis of 39 randomized studies on hypertensive LVH
regression performed in the last decade shows that (i) defini-
tion of LVH phenotype is extremely variable and based on as
many as 19 different echocardiographic criteria; (ii) no clini-
cally oriented information on LVH regression rates or changes
in LV geometrical patterns, as well as on target BP achieved
during treatment, is provided by the majority of these studies.
These findings make two final considerations necessary.
First, the clinical management of LVH would benefit from
adoption of a definition based on reference thresholds rec-
mended by scientific societies, rather than on a variety of
criteria arbitrarily chosen by research groups. Second, therapeu-
tic achievement of LVH regression might be improved by
using those thresholds as targets to be reached in clinical
practice.

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1. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left
ventricular mass and geometry to morbidity and mortality in uncomplicated
2. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications
of echocardiographically determined left ventricular mass in the Framingham
3. Bikkina M, Levy D, Evans JC, Larson MG, Benjamin EJ, Wolf PA, Castelli WP. Left
ventricular mass and the risk of stroke in an elderly cohort: the Framingham Heart
5. Schillaci G, de Simone G, Reboldi G, Porcellati C, Devereux RB, Verdecchia P.
Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L,
Rynkiewicz A, Schmieder RE, Benetier JF, Zannad F, Vahanian A, Camm J,
De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C,
Helleson J, Kristensen SD, McGregor K, Sechtem U, Silbers J, Tendera M,
Widimsky P, Zornamoro JL, Erdine S, Kivnick W, Agabiti-Rosei E, Ambrosioni E,
Lindhof LH, Viglimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E,
Bertomeu V, Clement D, Erdine S, Fassan C, Gatta Di Lepi G, Mallion JM, Manolis AJ,
7. Koren MJ, Ulin RJ, Koren AT, Laragh JH, Devereux RB. Left ventricular mass
8. Muiens ML, Saltetti M, Rizzoni D, Castellano M, Donato F, Agabiti-Rosei E.
implications of baseline echocardiographic features and their serial changes in
11. Verdecchia P, Angeli F, Bortignon C, Gattobigio R, de Simone G, Devereux RB,
12. Kloner RA, Sowers JR, DiBona GF, Gaffney M, Wein M. Effect of amiodipine on
13. Liebson PR, Grandits GA, Dianzumba S, Pirneis RJ, Grimm RH Jr, Neaton JD,
ramipril is more effective than the beta-blocker atenolol in reducing left ventricular mass in hypertensive patients. Results of the RACE (ramipril cardioprotective evaluation) study on behalf of the RACE study group. J Hypertens 1995; 13:1325–1334.
16. Gottardi JS, Reda DJ, Massie BM, Materson BJ, Williams DW, Anderson RJ.
Effect of single-dose therapy on reduction of left ventricular mass in mild to
17. Papademetriou V, Gottardi JS, Narayan P, Cushman WG, Zachariah PK,
Gottardi JS, Chace GA. Hydrochlorothiazide is superior to isradipine for reduction of left ventricular mass: results of a multicenter trial. The Isradipine Study Group. J Am Coll Cardiol 1997; 30:1802–1808.
Schuurman HV, van der Veer E, Lie KL, Meyboom-de Jong B. Effects of amiodipine
and lisinopril on left ventricular mass and diastolic function in previously
Iarussi D, Iacono A. Effects of losartan on hypertension and left ventricular mass: