Antihypertensive and cardiovascular effects of combined blockade of renin-angiotensin system with ACE inhibitor and angiotensin II type 1 receptor blocker in hypertensive patients: A 24-week randomized controlled double-dummy trial

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ABSTRACT: Background. In this study the effects of 24 weeks losartan and ramipril treatment, both alone and in combination, on blood pressure and left ventricular mass (LVM) and function, have been evaluated in hypertensives.

Methods. 57 hypertensives with stage 1 and 2 essential hypertension were included. After 4 weeks run in, a randomized double-blind, 3 arm, double dummy, independent trial was used. All patients were randomly allocated to 3 treatment arms consisting of losartan (50 mg/daily), ramipril (5 mg/daily), and combined (losartan 50 mg/ramipril 5 mg/daily) for 24 weeks. LVM, LVM/h^2 and other echocardiographic measurements, BUN, creatinine and clearance and potassium were determined after run in and 24 weeks.

Results. All groups were comparable for gender, age, BMI, BP and LVM. The prevalence of baseline left ventricular hypertrophy (LVH) was not significantly different among 3 groups. At the end of treatment, a significant (p<0.05) reduction in SBP, DBP, MBP, LVM and LVM/h^2 were observed in all groups. The absolute and percent reduction in LVM/h^2 were significantly higher in combined than losartan or ramipril groups and also in hypertensives with LVH. No significant change in absolute and percent reduction of SBP, DBP and MBP were found.

Conclusions. These data indicate an additional cardioprotective effect of dual blockade of RAS in hypertensive patients with and without left ventricular hypertrophy. (Heart International 2006; 2: )

KEY WORDS: Ace-inhibitors, Angiotensin II receptor blockers, Left ventricular geometry and function

INTRODUCTION

Impairment in left ventricular geometry and function represents a strong predictor for cardiovascular mortality and the occurrence of myocardial infarction, heart failure and stroke in hypertensive patients and general population (1, 2) Accordingly, reduction in left ventricular mass and regression of left ventricular hypertrophy (LVH) is today one of the most important goals of antihypertensive therapy (3, 4). Disproportional accumulation of fibrous tissue is a major characteristic of the adverse structural remodelling of cardiac tissue in hypertensive subjects. An increase in fibrillar collagen deposition determines a rise of interstitial and perivascular fi-
brosis in cardiac ventricles (5). The increased collagen and unchanged or insufficient degradation by collagenase (6) has been reported to promote systolic dysfunction, myocardial stiffness and abnormalities in diastolic ventricular filling and relaxation (7). Hemodynamic and non hemodynamic factors play a main role in the collagen turnover in hypertension (8, 9). Experimental data suggest that Angiotensin II stimulates fibroblast-mediated collagen synthesis (10, 11) independently of mechanical load either directly or via specific growth factors (12) and inhibits collagenase.

Even if antihypertensive drugs reverse left ventricular hypertrophy (LVH) by lowering blood pressure (13), meta-analyses of clinical trials have demonstrated that ACE-inhibitors (ACEi) and A-II type 1 receptor blockers (ARB) decrease left ventricular mass most effectively than other antihypertensive drugs (14). Moreover, some recent studies have reported that the combination of two agents, ACEi and ARB, that inhibit two consecutive renin-angiotensin-system (RAS) steps, promotes a decrease in myocardial fibrosis and left ventricular hypertrophy (15-18). This effect is due to a diminished AT1 receptor activation by a decreased Angiotensin II production. Other data indicate that administration of ACEi may be able to reduce the collagen content with consequent improvement of diastolic filling (16). Clinical data, comparing ACEi and ARB therapy in hypertensive heart disease, indicate that ARB have equivalent effects to ACEi on blood pressure and left ventricular hypertrophy (19), and these actions seem partially independent of their hemodynamic effects (8). In addition, experimental and clinical studies indicate that the combination of low doses of ACEi and ARB have a synergic and most effectiveness on left ventricular hypertrophy (20, 21). These effects might explain a better cardioprotection attributed to ACEi on blood pressure and left ventricular hypertrophy (19), and these actions seem partially independent of their hemodynamic effects (8). In addition, experimental and clinical studies indicate that the combination of low doses of ACEi and ARB have a synergic and most effectiveness on left ventricular hypertrophy (20, 21). These effects might explain a better cardioprotection attributed to ACEi and ARB than other antihypertensive drugs. Although a combination of ACEi and ARB treatment seems attractive, thus far limited data have emerged to support such as strategy.

Accordingly, the main goal of the present study was to determine the effects of 24 weeks’ losartan and ramipril administration on measurements of left ventricular geometry and function in hypertensive patients. For this reason hypertensive subjects were allocated randomly to 24 weeks of treatment with ACEi and ARB alone or in combination.

SUBJECTS AND METHODS

Patients

Subjects eligible for the study were screened for arterial hypertension at the antihypertensive center of the Department of Internal Medicine, University of Palermo, Italy. Subjects with a casual systolic blood pressure (SBP) ≥ 140 mmHg and < 180 mmHg and/or with casual diastolic blood pressure (DBP) ≥ 90 mmHg and < 110 mmHg obtained with a standard sphygmomanometer after 5 min of rest on three independent occasions, were invited to our day hospital for a detailed medical examination including history taking, physical, routine laboratory and echocardiographic examination. Exclusion criteria included the presence of any form of secondary hypertension; stage III essential hypertension, any irreversible end organ damage due to arterial hypertension; metabolic bone disease, hyperthyroidism, cardiovascular disease, diabetes, dyslipidemia, hepatic disease, alcoholic liver disease, malignants. Accordingly, from a large number of hypertensives, we established three groups of patients single matched for age, gender, body mass index (BMI), SBP and DBP. Fifty-seven patients fulfilled the selection criteria and baseline characteristics of the study participants are given in Table I.

Study design and active treatment

Each patient gave a written consent after having received a detailed description of the study procedure. The study was approved by the Ethics Committee of our Institution. Multiple comparisons power analysis was performed to determine sample size. The primary endpoint was considered the level of TGF-β1 changes and sample size was computed basing on the following assumptions: α = 0.05, power of at least 0.80 (β error equal or below 0.20), a minimum detectable difference of 3.00 with a standard deviation of 2.00 (minimum detectable difference.standard deviation =1.5). The total sample size resulted in 57 subjects (19 subjects for each of the three arms); it achieved 83% power using the Hsu (With Best) multiple comparison test at 0.05000 significance level.

This study was a randomized, double-blind, three-arm double-dummy independent trial. It was planned and conducted according to the revised recommenda-
Fig. 1 - Trial profile.

TABLE I - EFFECTS OF TREATMENTS ON BLOOD PRESSURE AND CLINICAL MEASUREMENTS

<table>
<thead>
<tr>
<th>Cases</th>
<th>Losartan 19</th>
<th>Ramipril 19</th>
<th>Combined 19</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
<td>Baseline</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>10/9</td>
<td>10/9</td>
<td>10/9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 7</td>
<td>56 ± 7</td>
<td>54 ± 8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.6 ± 4.9</td>
<td>31.2 ± 4.8</td>
<td>29.7 ± 4.3</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>162 ± 7</td>
<td>133 ± 5*</td>
<td>159 ± 7</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>94 ± 6</td>
<td>82 ± 7*</td>
<td>98 ± 9</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>116 ± 8</td>
<td>100 ± 6*</td>
<td>118 ± 9</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>42 ± 9</td>
<td>42 ± 8</td>
<td>37 ± 9</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.01 ± 0.2</td>
<td>1.03 ± 0.2</td>
<td>0.99 ± 0.1</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>89 ± 14</td>
<td>87 ± 17</td>
<td>93 ± 9</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.5 ± 0.3</td>
<td>4.6 ± 0.6</td>
<td>4.6 ± 0.4</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. MBP: Mean blood pressure. BUN: Blood Urea Nitrogen.
*p< 0.05 vs baseline
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double-dummy, so each group received two tablets (one pharmacologically active plus placebo, except the group that received two pharmacologically active drugs). Both placebo and active drug tablets were indistinguishable but for a letter label. Severe adverse reactions were monitored to enable the study to be stopped early if they emerged. The patient code was revealed to the clinical researchers once recruitment, data collection, laboratory analyses and statistical analysis were completed. No patient dropped out of the study, so all data of all patients were collected and analysed. An independent biostatistics expert analysed data and performed inferential analysis. All data analysis was carried out according to a pre-established analysis plan.

The patients attended the clinic for a total of eight study visits: at 4 and 2 weeks before randomization, at randomization (week 0), and at 1, 6, 12, 18 and 24 weeks after randomization. At each visit blood pressure was measured in the morning after 5 min of rest, about 24 hours after the previous drug administration. Sitting blood pressure was measured three times with an interval of about 2 min, and the mean was calculated. Mean blood pressure (MBP) was calculated by the formula DBP plus 1/3 of pulse pressure. At 0 and 24 weeks after randomization, both biochemical and echocardiographic measurements, circulating TGFβ1, PIP and PIIIP were determined.

Measurements

Patients underwent a general analytical laboratory parameters profile including BUN, creatinine and clearance, glycemia, electrolytes (serum sodium, potassium, chloride), by routine laboratory methods.

Echocardiographic measurements

All patients underwent an echocardiography examination M and B-mode, by a computerized echocardiography (ESAOTE, Italy) for the determination of following parameters: left ventricular telediastolic internal diameter (LVIDd), interventricular septum (IVSTd), and posterior wall thickness (PWTd). The Penn convention was used to calculate left ventricular mass (LVM). LVM was normalized for height to the 2.7 power (23). Accordingly, all the hypertensives with LVM/h^2.7 ≥ 50 g/m^2.7 for men and ≥ 47 g/m^2.7 for women were considered to have left ventricular hypertrophy (LVH). The prevalence of hypertensives with LVH into three treatment groups was not significantly different (Losartan group n. 10/19; Ramipril group n.10/19; Combined treatment group n.11/19). The relative wall thickness (RWT) by formula (IPWTd/LVIDd)x2 was also calculated. Ejection fraction from left ventricular end-diastolic and end-systolic volumes was measured from the apical four chamber view, using the ellipsoidal single-plane algorithm. Mean ejection fraction was automatically calculated by the echocardiographic processing system. In our laboratory the ejection fraction calculated over five consecutive beats permitted optimal reproducibility and accuracy (24).

LV relaxation and filling were evaluated by pulsed-wave Doppler interrogation of the LV inflow tract from the apical four-chamber view, with the sample volume placed at the tips of the mitral valve. After a stable signal of the transmitral flow velocity was obtained, the Doppler cursor was moved toward the LV outflow tract in the apical five-chamber view for recording both mitral and aortic signals, including the closing click of the aortic valve and the opening click of the mitral valve. Doppler signals were recorded at high speed (80-120mm/s) with the subjects in held expiration. An average of five beats was used for analysis.

Isovolumic relaxation time (IVRT) was calculated as the time from the closure click of the aortic valve to the opening click of the mitral valve. When either the closing or opening click was not identified, the time from the end of the aortic flow to the onset of mitral flow from the continuous wave interrogation of the LV inflow-outflow tract was used. Peak early transmisitr flow velocity (E), peak late transmisitr flow velocity (A), and the deceleration time of E velocity (DTE) were measured at the tips of mitral leaflets at the maximum amplitude of E velocity. DTE was measured as the time from peak E velocity to the time when E wave descent intercepts the zero line.

Statistical analysis

Data are expressed as mean value ± standard deviation. Non parametric tests were performed to test null hypothesis and two-sided value of p < 0.05 indicated a statistical significant difference. The Wilcoxon signed ranks test was performed to compare data at baseline and after treatment within groups. Groups’ data both at
baseline and after treatment changes were compared by the Kruskall-Wallis test used as a non-parametric alternative to the one way ANOVA. Pairwise comparisons between groups were performed using the Conover-Inman method when the Kruskall-Wallis indicated a significance among groups.

RESULTS

No significant differences in baseline age, BMI, SBP, DBP, MBP, routine biochemical measurements and echocardiographic measurements were observed for the losartan, ramipril and combination groups (Tabs. I, II).

Significant (p<0.05) decrease in SBP, DBP, MBP, total and indexed LVM values were observed in all the groups at the end of treatment compared to baseline values. In all groups no significant changes in biochemical measurements and in the remaining echocardiographic parameters were found at the end of treatment (Tabs. I, II). Figure 2 shows the responses of LVM/h2.7 values of individuals to the three treatments.

In the combination therapy group a significant increase in the absolute reduction of LVM/h2.7 (p<0.05 vs losartan; p<0.001 vs ramipril) was found. The percent reduction in LVM/h (p<0.05 vs losartan; p<0.03 vs

<table>
<thead>
<tr>
<th>TABLE II - EFFECTS OF TREATMENTS ON ECHOCARDIOGRAPHIC PARAMETERS</th>
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<tbody>
<tr>
<td><strong>Cases</strong></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>LVId (mm)</td>
</tr>
<tr>
<td>IVStd(mm)</td>
</tr>
<tr>
<td>PWTd (mm)</td>
</tr>
<tr>
<td>RWTr ([PWTd / LVId]x2)</td>
</tr>
<tr>
<td>LVM (g)</td>
</tr>
<tr>
<td>LVM/h2.7 (g/m2.7)</td>
</tr>
<tr>
<td>LVEF (%)</td>
</tr>
<tr>
<td>E/A velocity ratio</td>
</tr>
<tr>
<td>DTE (ms)</td>
</tr>
<tr>
<td>IVRT (ms)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE III - ABSOLUTE AND PERCENT REDUCTION (∆) LEFT VENTRICULAR MASS AND BLOOD PRESSURE IN THE THREE GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
</tr>
<tr>
<td><strong>Δ LVM/h2.7 (g/m2.7)</strong></td>
</tr>
<tr>
<td><strong>Δ LVM/h2.7 (%)</strong></td>
</tr>
<tr>
<td><strong>Δ SBP (mmHg)</strong></td>
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<tr>
<td><strong>Δ SBP (%)</strong></td>
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<tr>
<td><strong>Δ DBP (mmHg)</strong></td>
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<tr>
<td><strong>Δ DBP (%)</strong></td>
</tr>
<tr>
<td><strong>Δ MBP (mmHg)</strong></td>
</tr>
<tr>
<td><strong>Δ MBP (%)</strong></td>
</tr>
</tbody>
</table>

LVM/h2.7: left ventricular mass normalized to height2.7. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. MBP: Mean blood pressure.
Kruskall-Wallis test:
‡ p < 0.05 vs Losartan § p < 0.03 vs Ramipril
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Ramipril) was also higher in the combination group. No significant changes in absolute and percent changes in SBP, DBP and MBP was detected between the three groups (Tab. III).

Table IV shows the effects of treatment on LVM, LVM/h².7 and on percent reduction of LVM/h².7 in a subset of hypertensives with baseline LVH.

LVM and LVM/h².7 were significantly (p< 0.05) reduced at the end of treatment in all groups. Percent reduction in LVM/h².7 was significantly higher in combined group than ramipril (p< 0.02) and losartan (p< 0.01). Hypertensives with normalized LVM was similar in all groups (losartan 6/10; ramipril 7/10; combined 7/11).

![Individual responses of LVM/h².7 over the 24 weeks' treatment with losartan, ramipril and the combined treatment.](image)

**Fig. 2** - Individual responses of LVM/h².7 over the 24 weeks’ treatment with losartan, ramipril and the combined treatment.

**Table IV - Effects of treatments on total and indexed left ventricular mass and on its percent reduction in hypertensives with baseline left ventricular hypertrophy**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Losartan 10</th>
<th>Ramipril 10</th>
<th>Combined 11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
<td>Baseline</td>
</tr>
<tr>
<td>LVM (gr)</td>
<td>203 ± 37</td>
<td>172 ± 31*</td>
<td>198 ± 30</td>
</tr>
<tr>
<td>LVM/h².7 (g/m².7)</td>
<td>58 ± 8</td>
<td>49 ± 8*</td>
<td>57 ± 8</td>
</tr>
<tr>
<td>Δ LVM/h².7 (%)</td>
<td>−16</td>
<td>−19</td>
<td>−27†‡</td>
</tr>
</tbody>
</table>

LVM: left ventricular mass. LVM/h².7: left ventricular mass normalized to height².7

Δ LVM/h².7: Percent reduction in left ventricular mass normalized to height².7

Kruskall-Wallis test:

* p<0.05 vs baseline; †p<0.02 vs ramipril; ‡ p<0.01 vs losartan

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TABLE IV - EFFECTS OF TREATMENTS ON TOTAL AND INDEXED LEFT VENTRICULAR MASS AND ON ITS PERCENT REDUCTION IN HYPERTENSIVES WITH BASELINE LEFT VENTRICULAR HYPERTROPHY

<table>
<thead>
<tr>
<th>Cases</th>
<th>Losartan 10</th>
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<tr>
<td>Δ LVM/h².7 (%)</td>
<td>−16</td>
<td>−19</td>
<td>−27†‡</td>
</tr>
</tbody>
</table>

LVM: left ventricular mass. LVM/h².7: left ventricular mass normalized to height².7

Δ LVM/h².7: Percent reduction in left ventricular mass normalized to height².7

Kruskall-Wallis test:

* p<0.05 vs baseline; †p<0.02 vs ramipril; ‡ p<0.01 vs losartan
All treatment regimens were generally well tolerated. Side effects were few and transient. Two patients complained of asthenia, two of cough and three of dizziness but treatments were not discontinued.

**DISCUSSION**

In the present study we hypothesized that complete inhibition of the RAS would be most beneficial in management of left ventricular geometry and function in hypertensive patients and might be achieved by a dual blockade with ACEi and ARB. To prove this hypothesis we compared the effects of three treatments (monotherapy with ACEi and ARB and its combination) on blood pressure, left ventricular mass and function in hypertensive subjects. This was an independent single-center trial which, compared with multicenter trials, may have some benefits, such as a simple design, strict implementation and constant analysis of clinical and laboratory data. This is the first study designed to analyze the effects of dual RAS blockade on left ventricular mass and function in hypertensives.

Our results indicate an interesting finding. In fact, a more marked reduction in total and indexed left ventricular mass without impairment in diastolic and systolic left ventricular function following the combination of ACEi and ARB than either drug alone has been found in hypertensive subjects. In fact, the reduction in LVM/h².7 after 6 months of combined therapy, was significantly higher than LVM/h².7 reduction obtained with both single treatment, both in total hypertensives and in the subset with baseline LVH. This reduction was associated to unchanged EF and to a favorable trend in the measurements of diastolic function. It is important to emphasize that this effect was obtained with strict blood pressure control in all the groups. This finding discounts the suggestion that the differences observed upon the reduction in LVM could be explained only by the systemic blood pressure effect.

Cardioprotection induced by combined therapy observed by us has been reported previously in experimental studies and in patients with hypertensive diastolic heart failure (25). The exact mechanism of this finding is not entirely known but emerging data indicate a strong relationship among Angiotensin II, collagen turnover and left ventricular geometry and function (26). Accordingly, our hypothesis about a better cardioprotective effect induced by combined RAS blockade might be related to the well known effects of Angiotensin II both on blood pressure, systemic and cardiac hemodynamics (27, 28) and on inflammatory markers (29). ACEi reduce Angiotensin II but do not completely block the RAS, since Angiotensin II may be produced via other non-ACE-mediated pathways. Blockade of AT1 by ARB may also reduce the unfavorable effects of Angiotensin II. This might also induce a higher available Angiotensin II to bind with AT2 receptors; the latter may lead to relevant antigrowth and antitissue proliferation actions (27, 28). In particular, ARB also suppress some atherogenesis markers, such as cell-adhesion molecules, tumor necrosis factor alfa and superoxide (29). A combination of both agents may be more effective clinically than either one alone and recent trials show promising results (30, 31).

In view of this, our data indicate that the additive cardioprotection obtained with a combined RAS blockade might be mediated through a concomitant reduction in collagen. This hypothesis might be supported by recent results indicating an important role of TGFβ1 and collagen in the occurrence of myocardial fibrosis. In fact, recent experimental studies have shown that improvement of myocardial stiffness may be due to an inhibition of collagen synthesis rather than to an enhancement of collagen degradation (32). Collagen synthesis is altered by load, activation of RAS, neurohumoral and growth factors. Chronic activation of the RAS increases extracellular matrix and fibrillar collagen, promoting myocardial stiffness and diastolic dysfunction. The use of treatment that blocks RAS might improve diastolic function through a normalization of fibrillar collagen (16). The Angiotensin II type receptor is the target of the RAS system and its activation promotes ventricular fibrosis and hypertrophy (33). Experimental data demonstrate that a combination of ACEi and ARB have additive favorable effects on ventricular structural abnormalities, diastolic dysfunction and collagen accumulation (34) that are independent of their antihypertensive effectiveness. These effects might be in part due to the decrease of reactive oxygen species (ROS) generation. In fact, All directly stimulates ROS production promoted by macrophage infiltration (35) and the blockade of macrophage infiltration stops the production of TGFβ1 (36) and extracellular matrix (37).
Finally, combined therapy was characterized by a good safety profile and it was also supported by maintained renal function, left ventricular function and by inconsistent change in potassium at the end of the treatment.

However, our study has some possible limitations. First, it did not have a placebo group; such group was not approved by the ethics committee because of the known cardioprotection of ACEi and ARB. This limitation is unlikely to affect our data because both monotherapies significantly reduced LVM. Secondly, we have not assessed the most appropriate dose of each drug in combination treatment. We do not know if a combination of reduced doses of both drugs could offer the same cardioprotection as did the dose we used. In view of this, Peters et al (38) reported that submaximal doses of ACEi and ARB, like we used, are able to induce in combination maximal inhibition of angiotensin II and provide maximal therapeutic efficacy. In addition another study showed that addition of an ARB to an ACEi is more effective than doubling ACEi dose (39). Nevertheless dual RAS blockade is a relatively new concept and some questions remained unanswered. The duration of action of different ACEi and ARB might influence the effect of different combinations. Moreover complete RAS suppression and thus a higher dose or a shorter dose interval might be needed to obtain organ protection where lower doses are sufficient to treat hypertension (40). Finally, it is possible that reduction in LVM/h^2.7 after combined therapy might be underestimated since not only hypertensive patients recruited by us had left ventricular hypertrophy.

Some clinical implications arise from the results of our study. First, combination treatment was well tolerated without evidence of hyperkaliemia after 24 weeks. This provided further evidence to suggest that the present practice of avoiding use of ACEi and ARB or both, to prevent renal impairment and hyperkaliemia, is no longer justified. However, careful observation is still recommended. In conclusion our data suggest that hypertensive patients with higher LVM may be considered a particular subset of hypertensives who may particularly benefit from complete RAS blockade. This indication might also improve the therapeutic strategy for cardioprotection in hypertensive subjects.

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