Three-Dimensional Echocardiographic and Magnetic Resonance Assessment of the Effect of Telmisartan Compared With Carvedilol on Left Ventricular Mass

A Multicenter, Randomized, Longitudinal Study

Domenico Galzerano, Paolo Tammaro, Luca del Viscovo, Diana Lama, Antonio Galzerano, Roberto Breglio, Bernardino Tuccillo, Giuseppe Paolisso, and Paolo Capogrosso

Background: The hypothesis that left ventricular hypertrophy regression in hypertension relates to blood pressure (BP) control and to non-antihypertensive activity of some drugs was tested by comparing the effects of telmisartan and carvedilol on 24-h mean ambulatory BP and left ventricular mass (LVM) regression, measured using three-dimensional echocardiography (3-DECHO) and magnetic resonance imaging (MRI).

Methods: A total of 82 patients with mild-to-moderate hypertension and an optimal echocardiographic acoustic window were randomized to receive once-daily telmisartan 80 mg or carvedilol 25 mg for 44 weeks.

Results: Ten patients withdrew from the study because office diastolic BP remained >90 mm Hg. The 24-h mean ambulatory systolic/diastolic BP reductions were similar in both treatment groups (telmisartan, from 159.6 ± 10.2/97.8 ± 5.4 to 128.6 ± 6.5/78.2 ± 5.8 mm Hg; carvedilol, from 157.8 ± 11.1/95.7 ± 11.9 to 128.2 ± 5.6/78.7 ± 5.2 mm Hg). However, night-time and last 6-h mean BP reductions were nonsignificantly greater with telmisartan. Using 3-DE, telmisartan (P < .001) and carvedilol (P < .001) progressively reduced LVM index by 21.97 ± 5.84 (15.7%) and 12.31 ± 3.14 (9.1%) g/m², respectively, at week 44. Similar magnitudes of reductions were observed using MRI (15.5% and 9.6%, respectively). Reductions in LVM index achieved with telmisartan were statistically superior to carvedilol (P ≤ .001).

Conclusions: The superior LVM regression with telmisartan versus carvedilol suggests telmisartan has a mechanism that may be beyond that of lowering BP in hypertensive patients. Am J Hypertens 2005;18:1563–1569 © 2005 American Journal of Hypertension, Ltd.

Key Words: Telmisartan, angiotensin II receptor blocker, carvedilol, β-blocker, left ventricular hypertrophy.

Left ventricular hypertrophy (LVH), a response to increased pressure or volume load, is widely acknowledged as a strong predictor of cardiovascular risk, especially in the hypertensive patient. Clinical studies have demonstrated LVH regression occurs after significant decreases in blood pressure (BP) with most antihypertensive agents. There is, however, the possibility that some agents, because of their mode of action, confer benefit in addition to that arising from BP control.

Angiotensin II is thought to promote myocyte cell growth, and aldosterone increases collagen content and stimulates development of myocardial fibrosis; hence the potential benefit of the targeting of the renin–angiotensin–aldosterone system (RAAS). A meta-analysis of clinical studies has demonstrated that angiotensin-converting en-
zyme (ACE) inhibitors bring about a greater regression of left ventricular mass (LVM) than β-blockers, calcium channel blockers, or diuretics, despite all agents having similar antihypertensive efficacies.\(^5\) The angiotensin II receptor blockers (ARB) also target the RAAS by binding to angiotensin II type 1 (AT\(_1\)) receptors.\(^6\) The mode of action of ARB allows the available angiotensin II, irrespective of whether produced via ACE or other enzymatic pathways (eg, chymase in the heart), to stimulate the AT\(_2\) receptors, which may confer target-organ protection. Telmisartan, an ARB with a long half-life of approximately 24 h,\(^7\) has been shown to reduce LVH in hypertensive patients.\(^8\)–\(^10\)

The purpose of this study was to compare the antihypertensive efficacy, measured using ambulatory BP monitoring (ABPM), and the effects of telmisartan and carvedilol on LVM, assessed by three-dimensional echocardiography (3-DECHO) and magnetic resonance imaging (MRI). Carvedilol is both a β-blocker and vasodilator.\(^11\) In addition to reducing BP, carvedilol reduces heart rate, contractility, and wall tension and has been shown to provide cardioprotection in animal models.\(^10\) The benefits of carvedilol compared with traditional β-blockers may be important in elderly patients.\(^12\)

**Methods**

**Study Population**

Male and female subjects ≥18 years of age with an optimal two-dimensional echocardiography (2-DECHO) acoustic window, sinus rhythm, and mild-to-moderate hypertension (office diastolic BP, 90 to 114 mm Hg at the end of a 2-week wash-out period at the start of the study) were eligible. Patients with a LVM index related to body surface (LVMI) >130 g/m\(^2\) in men and >110 g/m\(^2\) in women (based on the upper 90\(^{th}\) percentile from a local reference group of 150 apparently healthy normotensive adults) were regarded as having LVH. Exclusion criteria were previous myocardial infarction or stroke, renal failure, chronic severe liver disease or congestive heart failure, left ventricular ejection fraction of <50\% determined by 2-DE. Pregnant or breast-feeding women were also excluded. Before enrollment, patients were required to provide informed consent.

**Study Design**

The study was approved by the local ethics committee. Enrollment and follow-up were performed at four institutions in Naples, Italy. Assessment of an optimal 2-DECHO acoustic window and treatment effects was conducted at four different centers, whereas 3-DECHO and MRI were each carried out at only one center. The team performing 3-DECHO and MRI was blinded to the patient’s treatment and differed from those prescribing open-label treatment. After a 2-week washout, run-in period, patients were assessed for eligibility by measuring BP. Eligible subjects were then randomized to once-daily treatment with telmisartan 80 mg or carvedilol 25 mg for 44 weeks; no other antihypertensive agents were allowed during the study. Clinic BP was measured at weeks 6, 18, and 32; any patient with a diastolic BP >90 mm Hg on any of these occasions was withdrawn from the study. Patients were instructed to take the study medication in the early morning except on days of clinic visits, when the medication was taken at the clinic immediately after BP measurement or the fitting of an ambulatory BP monitoring (ABPM) device. After completion of the 44 weeks of treatment, 3-DECHO, MRI, and ABPM were repeated. Standard blood tests and electrocardiography were performed at baseline and the end of active treatment. Adverse events were monitored throughout the study by a clinical examination.

**ABPM**

An oscillometric SpaceLabs 90207 monitor (SpaceLabs Inc., Redmond, WA) programmed to take measurements at 15-min intervals throughout the 24-h BP monitoring period was used, with recording starting between 9 and 11 AM. In cases in which an arm circumference exceeded 32 cm, a broad cuff was used. The device was checked against a mercury sphygmomanometer by a Y-tube. Data for ABPM with ≥85\% likely readings were analyzed. The 24-h period was divided into daytime (8 AM to 8 PM) and nighttime (8 PM to 8 AM).

**Echocardiography**

Preliminary assessment of an optimal 2-DECHO acoustic window on a four-grade scale (poor, sufficient, good, optimal) was performed using an Agilent Sonos 5500 echocardiograph (Philips Medical Systems, Eindhoven, The Netherlands) or ATL 5500 (Philips Medical Systems). All baseline and end-of-treatment 3-DECHO evaluations of LVMI were carried out at the Three-Dimensional Echocardiography Laboratory, Division of Cardiology, San Gennaro Hospital, Naples, Italy, using an Agilent Sonos 5500 echocardiograph and harmonic fusion imaging mode with a S3 transducer. An electromagnetic spatial locator was attached to the transducer and interfaced with the compact 3-DECHO cardiac imaging system (TomTec, Munich, Germany). With the patient in the left recumbent position, freehand image acquisition was performed from an apical window. Starting from the posterior border of the left ventricle, when the posterior wall had completely disappeared, the transducer was tilted slowly in fan-like manner across the heart toward the anterior border of the left ventricle; the entire left ventricle was encompassed by collecting 30 2-DECHO slices. The patient was instructed to avoid breathing during data acquisition. Acquired data were digitally stored, with the workstation acquiring the 2-DECHO video information at frame rates of 25 or 50 Hz (Echocan 4.2 software, TomTec). The transducer’s three-dimensional spatial orientation was determined using an electromagnetic locator system. This facilitated designa-
tion of spatial Cartesian coordinates to every frame (resolution/accuracy of the locator system: translation accuracy 0.18-cm root mean square; orientation accuracy 0.5 degrees root mean square). Electrocardiography and respiratory triggering enabled compensation for changes in the cardiac cycle; breath-held acquisitions were performed within 2.30 min (average, 2.07 ± 0.55 min).

**Echocardiography Analysis**

Echoview 4.2 TomTec software was used to analyze the 3-DECHO images, with LVM being calculated by disk summation. The left ventricle was divided into multiple equidistant, parallel, transverse, short-axis cutting planes (7 mm) from the atroventricular groove to the apex; the papillary muscles were not included. On each slice, the endocardium and epicardium were traced, with the computer measuring the area between them and an inherent computer program calculating the volume. The total left ventricular volume was obtained by adding the values of the individual slices, and the total myocardial mass was derived by multiplying the myocardial wall volume (mL) by tissue specific density 1.05 (g/cm³).

**MRI**

All MRI imaging, using a Magnetom Symphony (Siemens Medical Systems, Erlangen, Germany), was performed ≤7 days after 3-DECHO examination. All patients were scanned while supine using a four-element, phased-array cardiac coil and prospective cardiac triggering. After vertical (two-chamber view of the left ventricle) and horizontal (four-chamber view) long-axis cine imaging, short-axis cine images of the left ventricle, from the base to the apex, were obtained by contiguous 6-mm thick sections, using true-fast imaging with steady-state precession with the following parameters: repetition time/echo time 57/2.4 ms; flip angle 65 degrees; matrix 256 × 144; field of view 267 × 240; and bandwidth 977/Hz/pixel. All cine MRI images were acquired with the breath held at the end of expiration.

**MRI Analysis**

The short-axis images were processed using a software package (MR Cardio Module, Tiani, Vienna, Austria) loaded on a J-VISION workstation (Tiani) to calculate left ventricular volumes. Endocardial contours, including the left ventricular myocardium, were semi-automatically traced twice. Myocardial left ventricular volumes were calculated by summation of the product (area × slice thickness) of all slices with multiplication of this volume by the specific density to give the LVM. Papillary muscles were excluded from the calculation.

**Statistical Analysis**

The power calculations using nQuery Advisor 4.0 gave the following results: a sample size of 34 in each group would have 80% power to detect a difference in means of 5 (the difference between group A and B), assuming that the common standard deviation is 7.143 using a two-group t test with a 0.05 two-sided significance level.

The echocardiographic and MRI evaluation of each patient was reviewed twice by the same observer to calculate intraobserver variability and by two independent observers to determine interobserver variability. One observer analyzed the 3-DECHO images once, blinded to the results of the second observer. A second observer analyzed the 3-DE images twice, with a 5-week interval between the two analyses and blinded to the results of the first analysis.

All data are expressed as mean ± SD. Statistical analysis was performed within treatment groups using a t test for unpaired data. A value of \( P < .05 \) was considered to be statistically significant.

**Results**

**Patient Demographics and Baseline Characteristics**

A total of 82 patients were enrolled (Table 1). There were no statistically significant differences between the treatment groups. Ten patients withdrew from the study because diastolic BP remained >90 mm Hg (five patients receiving carvedilol and three receiving telmisartan at week 6, and one patient in each group at week 18) and two patients because of dizziness. A total of 70 patients completed the study, with the majority displaying LVH. Concomitant therapy was low: five patients in the telmisartan group and four in the carvedilol group were receiving statins, and one patient in the carvedilol group was receiving levothyroxine.

**Antihypertensive Activity**

Use of ABPM yielded a mean of 94% successful readings at baseline and end of active treatment. Significant reductions in 24-h mean systolic BP and diastolic BP were achieved with telmisartan \( (P < .001) \) and carvedilol \( (P < .001) \) after 44 weeks of treatment (Fig. 1). For telmisartan, 24-h mean systolic/diastolic BP were reduced from 159.6 ± 10.2 / 97.8 ± 5.4 to 128.6 ± 6.5 / 78.2 ± 5.8 mm Hg and for carvedilol from 157.8 ± 11.1 / 95.7 ± 11.9 to 128.2 ± 5.6 / 78.7 ± 5.2 mm Hg; the differences between treatments were not statistically significant. The differences in reduction of mean daytime SBP and DBP did not vary significantly between treatment groups. Night-time and last 6-h reductions with telmisartan were numerically greater than those achieved with carvedilol.

For telmisartan, baseline and end-of-treatment pulse rates were 74.8 ± 6.8 and 73.7 ± 7.1 beats/min, respectively. In the carvedilol group, pulse rate fell 67.8 ± 7.1 to 61.2 ± 7.4 beats/min after treatment.

**Changes in LVM**

After treatment, telmisartan and carvedilol brought about reductions in LVM (Fig. 2, 3). In the telmisartan group, 3-DECHO-evaluated LVM was reduced by 21.97 ± 5.84 g/m² and MRI-evaluated LVMI by 22.02 ± 5.92 g/m²,
Table 1. Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Telmisartan</th>
<th>Carvedilol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (n)</td>
<td>24/12</td>
<td>23/11</td>
</tr>
<tr>
<td>Age (y)</td>
<td>59.0 ± 9.2</td>
<td>60.0 ± 10.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.6 ± 3.1</td>
<td>27.1 ± 3.6</td>
</tr>
<tr>
<td>Statin treatment (n)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Duration of hypertension (y)</td>
<td>6.8 ± 6.9</td>
<td>7.4 ± 7.3</td>
</tr>
<tr>
<td>Clinic BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>159.6 ± 10.2</td>
<td>157.8 ± 11.1</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>97.8 ± 5.4</td>
<td>95.7 ± 11.9</td>
</tr>
<tr>
<td>Ambulatory BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h mean SBP (mm Hg)</td>
<td>159.6 ± 10.2</td>
<td>157.8 ± 11.1</td>
</tr>
<tr>
<td>24-h mean DBP (mm Hg)</td>
<td>97.8 ± 5.4</td>
<td>95.7 ± 11.9</td>
</tr>
<tr>
<td>Daytime mean SBP (mm Hg)</td>
<td>168.0 ± 11.0</td>
<td>169.0 ± 13.0</td>
</tr>
<tr>
<td>Daytime mean DBP (mm Hg)</td>
<td>104.0 ± 7.1</td>
<td>106.0 ± 7.7</td>
</tr>
<tr>
<td>Night-time mean SBP (mm Hg)</td>
<td>140.0 ± 11.4</td>
<td>138.0 ± 12.8</td>
</tr>
<tr>
<td>Night-time mean DBP (mm Hg)</td>
<td>82.2 ± 6.9</td>
<td>79.4 ± 8.6</td>
</tr>
<tr>
<td>Last 6-h mean SBP (mm Hg)</td>
<td>144.0 ± 9.8</td>
<td>142.0 ± 12.0</td>
</tr>
<tr>
<td>Last 6-h mean DBP (mm Hg)</td>
<td>84.5 ± 7.5</td>
<td>83.0 ± 8.4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74.8 ± 6.8</td>
<td>73.7 ± 7.1</td>
</tr>
<tr>
<td>LVH present (n)</td>
<td>30 (83%)</td>
<td>29 (85%)</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-DECHO</td>
<td>139.50 ± 12.87</td>
<td>134.58 ± 15.59</td>
</tr>
<tr>
<td>MRI</td>
<td>141.83 ± 13.05</td>
<td>137.16 ± 17.70</td>
</tr>
</tbody>
</table>

BP = blood pressure; 3-DECHO = three-dimensional echocardiography; DBP = diastolic blood pressure; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; MRI = magnetic resonance imaging; SBP = systolic blood pressure.

representing regressions of 15.7% and 15.5%, respectively. In the carvedilol group 3-DE-evaluated LVMI was reduced by 12.31 ± 3.14 g/m² and MRI-evaluated LVMI by 13.21 ± 4.65 g/m², representing regressions of 9.1% and 9.6%, respectively. The 3-DE underestimated LVMI slightly compared with MRI; the difference was not statistically significant. The effect of telmisartan measured using both 3-DE and MRI, was significantly superior to that of carvedilol (P = .0001). Interobserver variabilities were 7% and 3% intraobserver variabilities were 4% and 3% for MRI and 3-DE, respectively. We detected LVH regression in 50% of telmisartan patients and in 31% of carvedilol patients with baseline LVH (LVMI ≥130 g/m² in men and ≥110 g/m² in women).

Safety

Telmisartan and carvedilol were well tolerated, with adverse events representative of ARB and β-blockers, respectively. Adverse events were generally mild to moderate. Two patients (one in each group) withdrew because of dizziness. In the final study group, one telmisartan patient experienced fatigue and asthenia, whereas four carvedilol patients experienced fatigue and asthenia, and one reported mild vertigo that spontaneously disappeared. No blood test abnormalities were detected during treatment.

Discussion

Regression of LVH is an important endpoint when considering the efficacy of antihypertensive agents, because LVH can adversely affect the quality of life by increasing cardiovascular morbidity and mortality.2 However a previously published meta-analysis shows that not all classes of antihypertensive drugs are equally effective in reversing LVH.3 This analysis also suggests that regression is not only caused by BP reduction but that other drug-related mechanisms may be involved.

Both telmisartan and carvedilol, given once daily as recommended for treatment of hypertension, provide effective 24-h BP control, although there has been no previous direct comparison.10–14 In addition, both drugs have been shown to bring about regression of LVM.10,14,15 Both drugs have shown to bring about LVH regression.8–10,15 In this study, telmisartan and carvedilol were effective in reducing clinic diastolic BP to <90 mm Hg and their efficacy was confirmed by 24-h ABPM. Recording BP over 24 h showed that antihypertensive activity of both drugs was sustained throughout the dosing interval, which is likely to result in LVM regression because of the persistent reduction in pressure load. However closer examination of ambulatory BP shows that telmisartan provided greater reductions in night-time BP and during the last 6 h. Although not statistically significant, this is likely to have an impact on LVM regression. Our study was not designed to assess antihypertensive activity, as only patients responding to monotherapy based on clinic BP were included. Nonetheless our data suggest that clinic BP measurement may not provide a true measure of BP control, and ABPM may be a more accurate measure of antihypertensive activity as demonstrated by Redon et al.16
Previous reports would suggest that ARB are more effective in reducing LVM because of their mechanism of action, namely the targeting of the RAAS. In comparative studies, valsartan, irbesartan, and losartan have been shown to produce greater LVH regression than atenolol.\textsuperscript{17–19} The most conclusive data for the benefit of ARB-based therapy comes from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study,\textsuperscript{20} which clearly showed that less severe LVH is associated with reduced cardiovascular morbidity and mortality. A sub-study of LIFE conducted in 969 patients demonstrated that losartan-based therapy (plus other agents except \(\beta\)-blockers as needed to reduce BP) brought about greater LVH regression than atenolol-based treatment.\textsuperscript{21} Doubt has recently been cast as to the suitability of atenolol, as a meta-analysis has revealed that despite no differences in BP lowering compared with other antihypertensive agents, mortality was high with atenolol.\textsuperscript{22}

Clinical studies have shown that there are pharmacodynamic differences between antihypertensive drugs within specific classes. In the case of ARB, telmisartan (unlike losartan) provides sustained 24-h BP control.\textsuperscript{13} Similarly the pharmacology of carvedilol and atenolol differ.\textsuperscript{12} Traditional \(\beta\)-blockers such as atenolol may not be as effective or as well tolerated as newer vasodilatory \(\beta\)-blockers such as carvedilol.

In our study, telmisartan was significantly more effective than carvedilol in reducing LVM, despite both drugs being equally effective in reducing 24-h mean ambulatory BP. The use of 3-DECHO in patients with an optimal 2-DECHO acoustic window avoided any inaccuracy because of the poor quality of images.\textsuperscript{23} The MRI technique is a highly accurate and reproducible method for the quantification of LVM.\textsuperscript{24} It is to be considered to be a “gold standard” and as accurate as 3-DECHO, in case of an optimal acoustic window, and is very well suited for follow-up studies evaluating changes in LVM.

The relatively small number of patients evaluated in our study may be regarded as a potential limitation. However, 3-DECHO assessment of LVM has been demonstrated to require fewer patients than 2-DECHO,\textsuperscript{25} and in our study the effect on LVM is also supported by MRI, which is considered to be superior to echocardiography in the general population.\textsuperscript{24} One of the important benefits of MRI is that it requires even smaller sample sizes.\textsuperscript{26,27} The sample size required to detect a 10-g change in LVM has been calculated to be nine in patients with heart failure.\textsuperscript{27} We recorded consistent results using the two techniques. This strongly supports the value of our observations, even if not obtained in a large patient population. Despite comparable BP reductions with telmisartan and carvedilol, we observed that telmisartan resulted in a significantly greater LVM regression. It should be noted that this is the first study to evaluate the effect of carvedilol using MRI.

Both treatments were well tolerated, with comparable incidences of adverse events. In addition, no changes in fasting blood glucose or lipid profile were observed.

\[\text{FIG. 1}\] Changes from baseline in 24-h, daytime, night-time and last 6-h mean ambulatory (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP) after treatment with telmisartan 80 mg once daily or carvedilol 25 mg once daily for 44 weeks.

\[\text{FIG. 2}\] Change in left ventricular mass index (\(\triangle\)LVM) measured using three-dimensional echocardiography at baseline and after treatment with telmisartan 80 mg once daily or carvedilol 25 mg once daily for 44 weeks. \(P < .0001\) vs carvedilol.
Further information as to whether structural and functional cardiac parameters are associated with clinical outcomes will be addressed in a substudy of The ONTARGET Trial Programme. Cardiac MRI is being performed on 300 patients before randomization and after 2 years of treatment with telmisartan or ramipril or both, or with placebo.

We conclude that the findings of our study support the hypothesis that the superior regression of LVM produced by telmisartan could be caused not only by the control of BP and superior control of BP at the end of the dosing interval.

Acknowledgments
We express our thanks to Michele A. Tedesco, MD, PhD for the review of the manuscript and to Giuseppe Signoriello, MD, for the review of statistical data.

References