Comparative Effects of Irbesartan Versus Amlodipine on Left Ventricular Mass Index in Hypertensive Patients with Left Ventricular Hypertrophy

Carlo Gaudio, MD, Fabio Massimo Ferri, MD, Marco Giovannini, MD, Giuseppe Pannarale, MD, Paolo Emilio Puddu, MD, Alessandro Vittore, MD, Maria Stella Fera, MD, Carmine Dario Vizza, MD, and Francesco Fedele, MD

Abstract: The aim of this study was to comparatively assess the effects of irbesartan and amlodipine monotherapies on left ventricular mass index (LVMI) in patients with mild to moderate untreated hypertension and echocardiographically determined left ventricular hypertrophy (LVH). Sixty hypertensive patients (35 men, 25 women; mean age, 52.8 years ± 12.6) with diastolic blood pressure (BP) ≥ 100 mm Hg were randomized to irbesartan 150 mg once daily or amlodipine 5 mg once daily for a 4-week titration period. Dosage of both drugs was increased to irbesartan 300 mg once daily or amlodipine 10 mg once daily in case of sitting diastolic BP still >90 mm Hg after the first 2 weeks of treatment. Dosage doubling was necessary in more than 50% of patients in both treatment groups. After the titration period, only the responders (sitting diastolic BP ≤ 90 mm Hg) entered a 5-month maintenance period. After 3 months, echocardiographically estimated LVMI decreased by 23.2% in the irbesartan-treated patients and 11.4% in the amlodipine-treated patients, with an adjusted mean difference of 11.8% in favor of irbesartan ($P < 0.0001$). After 6 months, it decreased by 24.7% in the irbesartan-treated patients and 13.0% in the amlodipine-treated patients, with an adjusted mean difference of 11.6% in favor of irbesartan ($P < 0.0001$).

Key Words: amlodipine, echocardiography, hypertension, irbesartan, left ventricular hypertrophy

(*J Cardiovasc Pharmacol*™ 2003;42: 622–628)

Although left ventricular (LV) hypertrophy (LVH) may be considered a physiologic response to increased blood pressure (BP) in hypertensive subjects, it becomes a pathologic response when associated with marked changes in the structure, mechanical properties, and biochemistry of hypertrophied myocytes, which, together with increased interstitial volume, may lead to impaired coronary microcirculation.[1–3] Several studies have established that LVH is a powerful BP-independent cardiovascular risk factor.[4,5] The presence of LVH, detected by electrocardiography or echocardiography, represents a risk factor for major cardiovascular events, including the development of coronary heart disease (angina, myocardial infarction, sudden death), arrhythmias, congestive heart failure, stroke, transient ischemic attacks, and intermittent claudication.[6] In addition, the ECG-detected impairment of LV diastolic function that occurs in hypertensive patients is a more recent indicator of LV compliance reduction, often followed by a reduction in LV systolic function. Therefore, an actual goal of an effective early antihypertensive therapy—besides normalizing BP level, improving cardiac conditions, and preventing cardiac complications—is to reduce LVH and improve LV diastolic function.

Ample evidence suggests that some but not all antihypertensive drugs can reverse LVH.[7–11] Preliminary studies confirmed the beneficial effect of LVH regression on cardiovascular morbidity and mortality,[12–16] and it is now well-recognized that optimal patient management requires an evidence-based choice of treatment determined by well-designed comparative studies.[17,18] Therefore, we designed this between-patient, open-label, blinded-observer, randomized study to compare the efficacy of irbesartan, a long-acting angiotensin (Ang) II AT_1 receptor antagonist, with that of amlodipine, a well-studied calcium antagonist of the dihydropyridine group, on LV mass (LVM) reduction in hypertensive patients with echocardiographically-determined LVH.[19] We employed a quality-control procedure throughout the study and took blind, randomized, centralized end-study readings of all echocardiograms.

METHODS

The study was carried out with the prospective, randomized, open, blinded end point design[20] to compare the effect of randomly allocated irbesartan 150 mg and amlodipine 5 mg,

From the Department of Cardiology, "La Sapienza" University of Rome (Drs Gaudio, Ferri, Giovannini, Pannarale, Puddu, Vittore, Vizza, and Fedele); and Department of Cardioscience, "S. Camillo-Forlanini" Hospital, Rome, Italy (Dr Fera).

Received for publication November 11, 2002; accepted May 28, 2003.

Reprints: Prof. Carlo Gaudio at Via Gregorio VII, 324 00165 Rome, Italy (e-mail: carlo.gaudio@tiscali.it).

both given orally once daily to patients with essential arterial hypertension and echocardiographically determined LVH. Dosage of both drugs could be doubled if BP did not reach the goal after the initial treatment trial.

The primary outcome measure was the change in LV mass index (LVMI). Secondary outcome measures were the change in systolic, diastolic, and mean BP, pulse pressure, heart rate (HR), interventricular septum (IVS) thickness, posterior wall (PW) thickness, and LV end-diastolic diameter (EDD).

Study Population

Patients of both sexes, aged younger than 80 years, with untreated essential arterial hypertension (sitting diastolic BP of 100–115 mm Hg) and LVH, defined as an echocardiographic LVMI > 134 g/m^2 in men or >110 g/m^2 in women,[21] were eligible for the study. Patients with secondary hypertension or cardiovascular conditions such as congestive heart failure, valvular or ischemic heart disease likely to produce dyskinesia, akinesia, or other disturbances of ventricular geometry, as well as those with any disease that could interfere with the study protocol, were excluded.

During a recruitment period of 24 months, 60 new white patients with hypertension (35 men and 25 women, aged 25–79 years; mean age ± SD, 52.8 years ± 12.6) with echocardiographically-determined LVH were enrolled in this double-center study. Thirty patients were randomized to irbesartan treatment and 30 to amlodipine.

The echocardiograms of all of the patients were of sufficient quality for quantitative evaluation. Echocardiographic data are expressed as mean values, obtained by blind end-study readings made by two observers. The characteristics of the patients at randomization are given in Table 1.

TABLE 1. Patient Characteristics at Randomization

Characteristic	Irbesartan (n = 30)	Amlodipine (n = 30)	*P* Value
Sex (M/F)	18/12	17/13	
Age (y)	50.5 ± 12.7	53.4 ± 13.7	NS
Weight (kg)	68.1 ± 8.04	69.6 ± 7.9	NS
Height (cm)	166.2 ± 7.7	168.2 ± 6.02	NS
Systolic blood pressure (mm Hg)	167.8 ± 10.6	168.1 ± 13.0	NS
Diastolic blood pressure (mm Hg)	107 ± 5.8	108.3 ± 5.4	NS
Pulse rate (beats/min)	77.2 ± 9	75.4 ± 8.5	NS
LVMI (g/m^2) by echocardiography	140.87 ± 13.7	135.6 ± 16.9	NS

Values expressed as mean ± SD.
LVMI, left ventricular mass index; NS, not significant.

Treatment Protocol

All patients who gave their informed consent entered a 2-week run-in period during which they received one single-blind placebo tablet each morning.

At the end of the run-in period, the patients with a sitting diastolic BP ≥ 100 mm Hg were randomly allocated to the irbesartan group or the amlodipine group. Treatments were started with irbesartan at the dose of 150 mg and amlodipine at the dose of 5 mg, both administered as one tablet at 8:00 AM. In the case of unsatisfactory BP control after 2 weeks (sitting diastolic BP > 90 mm Hg), the dosage could be doubled. At the end of the fourth week, patients with a sitting diastolic BP ≤ 90 mm Hg who did not experience any adverse drug effect followed the same randomized treatment at the titrated dosage for a further 5 months. Patients with a sitting diastolic BP > 90 mm Hg were removed from the study.

Measurements

All measurements were made between 3:00 PM and 6:00 PM, ie, approximately 7–10 hours after morning drug intake. Patients underwent a thorough clinical examination (including BP and HR measurements and assessment of spontaneously reported side effects) at the end of the placebo run-in period, after 2 and 4 weeks, and at the end of each of the following 5 months. On each occasion, two BP readings (with a 2-minute interval between them) were made with use of a mercury sphygmomanometer (Korotkoff phase 5 for diastolic BP) after the patient had been in a sitting position in a quiet room for 10 minutes; the mean of the two readings was recorded. Heart rate was calculated by means of radial pulse palpation for 30 seconds immediately after the BP readings.

Echocardiograms were obtained at the end of the placebo run-in period and after 3 and 6 months of treatment. All echocardiographic tracings were obtained by the same operator, who was not involved in the study. The echocardiographic tracing plates were coded without mention of the treatment and, at the end of the study, were independently interpreted by two investigators who were blinded to the treatment group and to the sequence of recording (time of visit unknown). For each variable, the mean values of the two readers were used.

Echocardiography

The echocardiographic images were obtained with use of a two-dimensional M-mode ultrasonoscope (Sim 7000 Challenge; Esaote Biomedica, Italy) and a 2.5-MHz transducer probe and were photorecorded at a paper speed of 50 mm/sec.

The M-mode echocardiographics of the left ventricle were taken in the long-axis view just below the tips of the mitral valve leaflets, a position showing continuous echoes from the septum and PW, in accordance with the recommendations of the American Society of Echocardiography.[22] The values obtained from an average of at least five cardiac cycles were calculated by each of the two readers.

The following universally accepted formula for calculating the M-mode LVM, based on the American Society of Echocardiography cube formula with the correction factor proposed by Devereux et al,[21] was used:

$$\text{LVM (g)} = 0.80 \times [1.04 \times (\text{LV EDD} + \text{IVS thickness} + \text{PW thickness})^3 - (\text{LV EDD})^3] + 0.6$$

where LV EDD is the internal EDD of the LV.

LVM was divided by the body surface area to obtain the LVMI (g/m^2). Left ventricular hypertrophy was prospectively defined by an LVMI > 134 g/m^2 body surface area in men or >110 g/m^2 in women.

Statistical Analysis

The sample size was estimated to have an 80% chance of detecting a difference of 8 g/m^2 (SD, 8) between irbesartan and amlodipine in the primary endpoint (ie, a change in the LVMI after 3 or 6 months of treatment), with an overall significance level of 5% (two-tailed test). A sample of 40 patients was deemed to be necessary. To correct for potential baseline discrepancies between the two randomized groups, we compared adjusted means by covariance analysis. This method combines regression and analysis of variance and yields more accurate results than just comparing raw means. Nevertheless, both crude and adjusted means were reported. For the primary variable of echocardiographically-measured LVMI, the baseline values were used as covariate and the treatment as factor. The baseline treatment interaction (homogeneity of regression slopes) was also tested before performing the analysis. All analyses were performed by using the Statistical Analysis System, version 8.01 (SAS, Cary, NC, U.S.A.). A *P* value less than 0.01 was considered significant.

RESULTS

Sixty patients with ECG-determined LVH, 35 men and 25 women, aged 25–79 years (mean age, 52.8 years ± 12.6), who had an average known duration of hypertension of 3.8 years, were included in the study. The characteristics of the patients at randomization are given in Table 1.

Eleven patients, six in the irbesartan group and five in the amlodipine group, could not be considered for the efficacy evaluation of the antihypertensive drugs because, after 4 weeks of treatment, they did not have sitting diastolic BP ≤ 90 mm Hg as required by the protocol. Another six patients discontinued the treatment because of side effects: one irbesartan-treated patient because of a doubtfully correlated headache and five amlodipine-treated patients because of leg edema ($n = 4$) and leg skin rash ($n = 1$). The analysis was therefore based on the data of 43 patients, 23 in the irbesartan group and 20 in the amlodipine group.

In the irbesartan group, 10 patients had the 150-mg treatment regimen and 13 patients needed to take the 300-mg dose. In the amlodipine group, nine patients had the 5-mg treatment, while 11 needed to be treated with the 10-mg dose. None of the patients took any additional antihypertensive drugs throughout the study.

Blood Pressure and Heart Rate

Systolic and diastolic BP were significantly reduced by irbesartan and amlodipine (Table 2). After 3 months of treatment, a small, nonsignificant difference between the two drugs was observed in systolic and diastolic BP, which decreased slightly more in the irbesartan group than in the amlodipine group (adjusted mean difference between irbesartan and amlodipine, 3.2% and 1.5%, respectively). After 6 months of treatment, the reductions in systolic BP was 15.2% in the amlodipine group and 18% in the irbesartan group; the reductions in diastolic BP were 19.4% and 22%, respectively.

Pulse pressure reduction was higher in the irbesartan group, even though the difference with the amlodipine group was not significant after 3 months (11.0% vs. 4.4%) and 6 months (10.9% vs. 7.5%).

After 6 months of treatment, HR was moderately increased in the amlodipine group and slightly decreased in the irbesartan group (4.3% and −1.4%, respectively; $P = 0.01$).

Left Ventricular Structure by Echocardiography

The mean values (±SD) of LVMI, IVS, and LV PW thickness, as measured by echocardiography, at baseline and after 3 and 6 months of treatment, are shown in Table 2, together with their related adjusted mean values (±SD), calculated by analysis of covariance.

The LVMI decreased in both groups, but more significantly in the irbesartan group than in the amlodipine group. After 3 months of treatment, the decreases were 23.2% in the irbesartan group and 11.4% in the amlodipine-treated patients, with an adjusted mean difference of 11.8% in favor of irbesartan ($P < 0.0001$).

At the end of the study, the actual decreases in the LVMI were 24.7% in the irbesartan group and 13.0% in the amlodipine-treated patients, with an adjusted mean difference of 11.7% in favor of irbesartan ($P < 0.0001$). Most of the drug-induced effects on LVMI therefore took place during the first 3 months of treatment. The reduction in LVMI was not significantly correlated with the decrease in systolic BP, diastolic BP, pulse pressure, or HR variations.

IVS and LV PW thickness decreased with both treatments, with irbesartan again significantly superior to amlodipine. The reductions in echocardiographically-measured IVS thickness in the irbesartan group were greater than those obtained in the amlodipine group after 3 months (adjusted mean difference, −22.3% vs. −14.2%; $P < 0.0001$) and 6 months (adjusted mean difference, –23.0% vs. –15.1%; $P < 0.0001$). Irbesartan was also superior to amlodipine in decreasing PW thickness, both after 3 months (adjusted mean difference, –14.3% vs. –6.9%; $P < 0.0001$) and 6 months of treatment (adjusted mean difference, –15.2% vs. –7.9%; $P <$

TABLE 2. Mean and Adjusted Values (± SD) of the Primary and Secondary Outcome Parameters at Baseline and After 3 and 6 Months of Treatment

	Actual Values			Adjusted Values					
	Baseline	3 mo	6 mo	3 mo	*P**	Δ	6 mo	*P**	Δ
Systolic blood pressure									
Amlodipine	163.8 ± 12.6	140.0 ± 7.6	138.8 ± 7.6	140.2 ± 5.8		−14.4%	139.0 ± 5.8		−15.2%
Irbesartan	165.9 ± 10.5	137.2 ± 6.0	136.5 ± 5.3	136.7 ± 5.7	0.048	−17.6%	136.0 ± 5.7	0.10	−18.0%
Diastolic blood pressure									
Amlodipine	106.3 ± 4.6	84.8 ± 3.8	85.3 ± 3.8	85.2 ± 3.4		−19.8%	85.7 ± 3.4		−19.4%
Irbesartan	105.7 ± 5.1	83.5 ± 3.8	82.8 ± 3.6	83.1 ± 3.3	0.048	−21.3%	82.5 ± 3.3	0.002	−22.0%
Mean blood pressure									
Amlodipine	125.4 ± 6.4	103.2 ± 4.4	103.1 ± 4.3	103.6 ± 3.0		−17.4%	103.5 ± 3.0		−17.5%
Irbesartan	125.7 ± 5.7	101.4 ± 3.3	100.7 ± 3.4	100.9 ± 3.0	0.01	−19.7%	100.3 ± 3.0	0.00	−20.2%
Pulse pressure									
Amlodipine	57.5 ± 10.7	55.3 ± 6.6	53.5 ± 6.9	54.9 ± 6.2		−4.4%	53.2 ± 6.2		−7.5%
Irbesartan	60.2 ± 9.7	53.7 ± 6.9	53.7 ± 5.5	53.6 ± 6.2	0.49	−11.0%	53.6 ± 6.2	0.82	−10.9%
Heart rate									
Amlodipine	74.2 ± 6.5	76.0 ± 6.6	76.3 ± 7.0	77.1 ± 2.6		3.9%	77.4 ± 2.6		4.3%
Irbesartan	76.3 ± 9.1	76.6 ± 9.3	76.2 ± 8.6	75.6 ± 2.6	0.06	−0.9%	75.2 ± 2.6	0.01	−1.4%
LVMI									
Amlodipine	137.8 ± 17.6	121.1 ± 17.0	118.8 ± 17.0	122.1 ± 9.5		−11.4%	119.8 ± 9.5		−13.0%
Irbesartan	141.4 ± 15.0	109.5 ± 12.1	107.3 ± 11.6	108.6 ± 9.5	<.0001	−23.2%	106.5 ± 9.5	<.0001	−24.7%
IVST									
Amlodipine	12.8 ± 0.9	11.7 ± 0.8	11.5 ± 0.9	11.0 ± 0.5		−14.2%	10.9 ± 0.5		−15.1%
Irbesartan	13.0 ± 0.8	11.1 ± 0.7	10.9 ± 0.6	10.1 ± 0.5	<.0001	−22.3%	10.0 ± 0.5	<.0001	−23.0%
LV EDD									
Amlodipine	54.0 ± 3.3	53.8 ± 3.6	53.7 ± 3.6	53.4 ± 1.0		−1.1%	53.3 ± 1.0		−1.2%
Irbesartan	53.3 ± 3.7	52.9 ± 3.6	52.8 ± 3.6	53.2 ± 1.0	0.47	−0.2%	53.1 ± 1.0	0.46	−0.3%
PWT									
Amlodipine	11.8 ± 0.9	11.0 ± 0.7	10.9 ± 0.7	11.0 ± 0.5		−6.9%	10.9 ± 0.5		−7.9%
Irbesartan	11.8 ± 0.6	10.1 ± 0.7	10.0 ± 0.7	10.1 ± 0.5	<.0001	−14.3%	10.0 ± 0.5	<.0001	−15.2%

IVST, Interventricular septum thickness; LV EDD, left ventricular end-diastolic diameter; PWT, posterior wall thickness; Δ, percentage variation.

0.0001). By contrast, LV EDD remained virtually unchanged in irbesartan and amlodipine treatments.

DISCUSSION

One of the main mechanisms used by the heart to compensate for a chronic increase in afterload, and thus wall stress, is to increase its wall thickness. Initially, this compensatory mechanism may offset the increase in afterload, but later, the development of LVH may have deleterious consequences.[1–2] In fact, LVH represents not only a compensatory response to the hemodynamic alterations, but also a process developed by the contribution of various factors related with neurohormonal events, aging, and genetics.[23–24]

In hypertension, LVH is a powerful and independent risk factor for cardiovascular morbidity and mortality.[3–5] Recently, the prevalence of LVH has been estimated to be 62% in patients with mild to moderate essential hypertension.[25] There is therefore a strong evidence that the normalization of LVM has become a desirable goal of an effective antihypertensive treatment.

The main finding of this randomized, controlled study in hypertensive patients with echocardiographically-determined LVH is that irbesartan appears to be more effective than amlodipine in reducing LVMI after 6 months of treatment, despite a similar effect on BP of the two drugs.

As in our previous studies,[26–27] we randomized only those patients satisfying the widely recognized echocardiographic criteria for LVH. Despite a more difficult selection of potential study participants, this choice leads to more firm conclusions regarding the ability of the drugs to induce not only a reduction in increased LVMI, but more specifically the reversal of LVH, defined according to standard criteria.[17,21]

Moreover, to avoid potential interference from additional antihypertensive drugs, only previously untreated hy-

pertensive patients were selected, and only the responders (diastolic BP ≤ 90 mm Hg) to an initial 4-week treatment with the randomized drug followed the same randomized treatment for a further 5 months. This procedure required doubling the doses of study medications in more than 50% of the patients in both treatment groups.

The interpretation of the results of this study is therefore straightforward, as it regards comparison of two monotherapies, an approach rarely followed in other studies. The Veterans Affairs Cooperative Study Group on Antihypertensive Drugs reported the effects of single-drug therapy on the LVM regression in patients with mild to moderate hypertension.[28] However, because the Veterans Affairs Cooperative study differed so much from our study (patients were all male and 58% were black) and was greatly flawed by the fact that 75%–80% of the participants in each group were lost to follow-up, great caution must be used in interpreting the results.

The study of Beltman et al compared the effects of amlodipine and lisinopril monotherapies on LVMI in patients with previously untreated mild to moderate hypertension.[29] The LVMI decreased significantly in both treatment groups, and a high therapeutic response was found (83% responded to the two monotherapies). In the last 10 years, some metaanalyses placed great emphasis on the finding that various classes of drugs are differently effective in reducing LVH.[7,10] These metaanalyses have been criticized mainly on the basis of their many methodologic flaws, but their conclusions were widely accepted and have recently been largely confirmed by a third metaanalysis performed by Schmieder et al, who considered only randomized studies using blind echocardiogram evaluations.[8] Of the 471 published reports, only 39 satisfied the predetermined study quality criteria: after adjustment for study duration, this metaanalysis indicated Ang-converting enzyme inhibitors and calcium antagonists as first-line candidates for reducing the risk associated with LVH.[8]

In the present study, we compared the effects on LVH regression of amlodipine, a long-acting calcium antagonist of the dihydropyridine group, and irbesartan, a long-acting Ang-II receptor antagonist. The efficacy of amlodipine in the treatment of hypertensive patients with LVH has already been demonstrated in previous studies.[30–33] These results are based primarily on the reduction of LV systemic wall tension that occurs after the decrease in systemic vascular resistance, but other factors independent of hemodynamic changes probably contribute to this process. One of these factors may be that sympathetic activity, which is important in the development of LVH, does not increase, and even decreases, during treatment with amlodipine.[30] In addition to a chronic increase in pressure and/or volume overload, the pathogenesis of LVH is linked to activation of the renin–angiotensin system, with excessive production of Ang II.[34–35] Apart from the well-known cleavage of Ang I by Ang-converting enzyme, alternative pathways exist for the formation of Ang II, and therefore a large amount of Ang II may be present in the heart.[36] Because the main actions of Ang II in human hypertension, cardiac cell growth and proliferation, are mediated via AT_1 receptor subtype, Ang II AT_1 receptor antagonists, the newest class of antihypertensive drugs, could be effective in terms of LVH regression.[37] Some recent studies assessed the antihypertensive effects of different Ang II receptor antagonists in patients with essential hypertension and also compared them with those of other classes of drugs.[38–41] Irbesartan (SR-47436, BMS-186295) is a potent, long-acting nonpeptide Ang II receptor antagonist with high selectivity for the AT_1 receptor subtype.[42]

In patients with mild to moderate hypertension, once-daily administration of irbesartan 150 or 300 mg provided effective 24-hour BP control. Irbesartan reduced BP to a similar extent as atenolol and enalapril and to a significantly greater extent than losartan.[43–45]

The results obtained in our study demonstrate that irbesartan causes a greater reduction in LVMI than does amlodipine in hypertensive patients with echocardiographically-determined LVH. In fact, the decrease in LVMI induced by irbesartan was significantly higher than that obtained with amlodipine. After 3 months of treatment, echocardiographically-estimated LVMI decreased by 23.2% in the irbesartan-treated patients and 11.4% in the amlodipine-treated patients, with an adjusted mean difference of 11.8% in favor of irbesartan ($P < 0.0001$). After 6 months, it decreased by 24.7% in the irbesartan group and 13.0% in the amlodipine group, with an adjusted mean differences of 11.6% in favor of irbesartan ($P < 0.0001$). Therefore, most drug-induced effects on LVMI took place during the first 3 months of treatment.

The IVS and LV PW thickness decreased with both treatments, with irbesartan again significantly superior to amlodipine; by contrast, LV EDD remained virtually unchanged with both treatments.

Both monotherapies reduced systolic and diastolic BP to a similar extent, with a nonsignificant greater effect in favor of irbesartan. Pulse pressure reduction was higher in the irbesartan group, but the difference compared with the amlodipine group was not significant. The HR was moderately increased in the amlodipine group and preserved in the irbesartan group (4.3% and –1.4%, respectively; $P = 0.01$).

As already demonstrated in previous studies,[38,46] the two treatments were differently tolerated. The incident of drug-related side effects was significantly higher in the amlodipine group than in the irbesartan group (16.67% vs. 3.33%), with an exclusive presence of ankle edema in the amlodipine group (13.33%).

CONCLUSIONS

Our findings are consistent with the main conclusions of several recent studies that assessed the efficacy of the Ang II AT_1 receptor antagonists on BP reduction and LVMI regression.[47–52] However, this is the first study that compared irbe-

sartan and amlodipine monotherapies in previously untreated hypertensive patients with echocardiographically-proven LVH. The extent of reduction in LVMI demonstrates that once-daily irbesartan is an effective and very well-tolerated antihypertensive agent for the treatment of hypertensive patients with LVH. These results suggest that irbesartan, and possibly Ang II AT_1 receptor antagonists, could play an important role in prevention of cardiovascular complications and regression of target organ damage.

ACKNOWLEDGMENT

The authors thank Professor Fabrizio Veglia (Torino, Italy) for expert advice on statistical methodology.

REFERENCES

1. Grossman W. Cardiac hypertrophy: useful adaptation or pathologic process? *Am J Med*. 1980;69:576–584.
2. Folkow B. The Fourth Volhaard Lecture: cardiovascular structural adaptation—its role in initiation and maintenance of primary hypertension. *Clin Sci Mol Med*. 1987;55:3S–22S.
3. Kannel WB, Levy D, Cupples LA. Left ventricular hypertrophy and risk of cardiac failure: insight from the Framingham study. *J Cardiovasc Pharmacol*. 1987;10:S135–S140.
4. McLenachan JM, Henderson E, Morris KL, et al. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. *New Engl J Med*. 1987;317:787–792.
5. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *New Engl J Med*. 1990;322:1561–1566.
6. Dunn FG, Pfeffer MA. Left ventricular hypertrophy in hypertension. *N Engl J Med*. 1999;340:1279–1280.
7. Dahlof B, Pennert K, Hansson L. Reversal of left ventricular hypertrophy in hypertensive patients. A meta-analysis of 109 treatment studies. *Am J Hypertens*. 1992;5:95–110.
8. Schmieder RE, Schlaich MP, Klingbeil AU, et al. Update on reversal of left ventricular hypertrophy in essential hypertension (a meta-analysis of all randomized double blind studies until December 1996). *Nephrol Dial Transplant*. 1998;13:564–569.
9. Jennings G, Wong J. Regression of left ventricular hypertrophy in hypertension: changing patterns with successive meta-analyses. *J Hypertens*. 1998;16:S29–S34.
10. Cruickshank J, Lewis J, Moore V, et al. Reversibility of left ventricular hypertrophy by different types of antihypertensive therapy. *J Hum Hypertens*. 1992;6:85–90.
11. Gosse P, Dallocchio M. La regression de l'hypertrophie ventriculaire gauche chez l'hypertendu. Paris, France: Editions Medecine Pratique; 1992.
12. Koren MJ, Ulin RJ, Laragh JH, et al. Reduction of the left ventricular mass during treatment of essential hypertension is associated with improved prognosis. *Am J Hypertens*. 1991;4:1A.
13. Yurenev AP, Dyakonova HG, Novikov ID, et al. Management of essential hypertension in patients with different degrees of left ventricular hypertrophy: multicentre trial. *Am J Hypertens*. 1992;5:182S–189S.
14. Levy D, Salomon M, D'Agostino RB, et al. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation*. 1994;90:1786–1793.
15. Muiesan ML, Salvetti M, Tizzoni D, et al. Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment. *J Hypertens*. 1995;13:1091–1105.
16. Verdecchia P, Schillaci G, Borgioni C, et al. Prognostic significance of serial changes in left ventricular mass in essential hypertension. *Circulation*. 1998;97:48–54.
17. Devereux RB. Do antihypertensive drugs differ in their ability to regress left ventricular hypertrophy? *Circulation*. 1997;95:1983–1985.
18. The Sixth Report of the Joint National Committee On Prevention. Detection, Evaluation and Treatment of High Blood Pressure (JNV VI). *Arch Intern Med*. 1997;157:2413–2446.
19. Kloner RA, Sower JR, Di Bona GF, et al, for the ACCT Study Group. Effect of amlodipine on left ventricular mass in the Amlodipine Cardiovascular Community Trial. *J Cardiovasc Pharmacol*. 1995;26:471–476.
20. Hansson L, Hedner T, Dahlof B. Prospective, Randomized, Open Blinded Endpoint (PROBE) study: a novel design for intervention trials. *Blood Press*. 1992;1:113–119.
21. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiography assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57:450–458.
22. Shan DJ, De Maria A, Kisslo J, et al. The Committee on M-Mode Standardization of the American Society of Echocardiography: recommendations regarding quantitation in M-Mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*. 1978;58: 1072–1083.
23. Kent RL, Mann DL, Cooper G. Signals for cardiac muscle hypertrophy in hypertension. *J Cardiovasc Pharmacol*. 1991;17:S7–S13.
24. Long CS, Kariya K, Karns L, et al. Sympathetic activity: modulator of myocardial hypertrophy. *J Cardiovasc Pharmacol*. 1991;17:S20–S4.
25. Zabalgoitia M. Left ventricular mass and function in primary hypertension. *Am J Hypertens*. 1996;9:55S–59S.
26. Gaudio C, Tanzilli G, Collatina S, et al. Evaluation of regression of left ventricular hypertrophy in hypertensive patients treated with captopril as assessed by magnetic resonance imaging. *Cardiologia*. 1992;37: 789–791.
27. Gaudio C, Tanzilli C, Ferri FM, et al. Benazepril causes in hypertension a greater reduction in left ventricular mass than does nitrendipine: a randomized study using magnetic resonance imaging. *J Cardiovasc Pharmacol*. 1998;32:760–768.
28. Gottdiener JS, Reda DJ, Massie BM, et al. Effect of single-drug therapy on reduction of left ventricular mass in moderate hypertension: comparison of six antihypertensive agents. *Circulation*. 1997;95:2007–2014.
29. Beltman FW, Heesen WF, Smit AJ, et al. Effects of amlodipine and lisinopril on left ventricular mass and diastolic function in previously untreated patients with mild to moderate diastolic hypertension. *Blood Press*. 1998;7:109–117.
30. Adalet K, Mercanoglu F, Orak E, et al. The effect of amlodipine on the mass and function of the left ventricle in patients with primary hypertension and left ventricular hypertrophy. *Curr Ther Res Clin Exp*. 1995;56: 607–614.
31. Fak AS, Okucu M, Tezcan H, et al. The effects of amlodipine on left ventricular mass and diastolic function in concentric and eccentric left ventricular hypertrophy. *J Cardiovasc Pharmacol Ther*. 1996;1:95–100.
32. Singh NK, Gupta SK, Agrawal BV. Left ventricular mass regression with amlodipine in elderly hypertensives. *Clin Exp Hypertens*. 1999;21: 113–119.
33. Islim IF, Watson RD, Ihenacho HN, et al. Amlodipine: effective for treatment of mild to moderate essential hypertension and left ventricular hypertrophy. *Cardiology*. 2001;96:10–18.
34. Sadoshima J, Izuno S. Molecular characterization of angiotensin II-induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblast. *Circulation*. 1993;73:413–423.
35. Schunkert H, Hense HW, Muscholl M, et al. Associations between circulating components of the renin-angiotensin-aldosterone system and left ventricular mass. *Heart*. 1997;77:24–31.
36. Urata H, Kinoshita A, Misono KS, et al. Identification of a highly specific chymase as the major angiotensin II-forming enzyme in the human heart. *J Biol Chem*. 1990;265:2348–2357.
37. Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med*. 1996;334:1649–1654.
38. Corea L, Cardoni O, Fogari R, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: a comparative study of the efficacy and safe against amlodipine. *Clin Pharmacol Ther*. 1996; 60:341–346.
39. Pool JL, Guthrie RM, Littlejohn TW III, et al. Weir MR Wilson TW, Wright J, Kassler-Taub KB, Reeves RA: Dose-Related Antihypertensive Effects of Irbesartan in Patients With Mild-to-Moderate Hypertension. *Am J Hypertens*. 1998;11:462–470.

40. Lacourciere Y, Lenis J, Orchard R, et al. A comparison of the efficacies and duration of action of the angiotensin II receptor blockers telmisartan and amlodipine. *Blood Press Monit*. 1998;3:295–302.
41. Ishimitsu T, Minami J, Yoshii M, et al. Comparison of the effects of amlodipine and losartan on 24-hour ambulatory blood pressure in hypertensive patients. *Clin Exp Hypertens*. 2002;24:41–50.
42. Cazaubon C, Gougat J, Bousquet F, et al. Pharmacological characterization of SR 47436, a new nonpeptide AT_1 subtype angiotensin II receptor antagonist. *J Pharmacol Exp Ther*. 1993;265:826–834.
43. Stumpe KO, Haworth D, Hoglund C, et al. Comparison of the angiotensin II receptor antagonist irbesartan with atenolol for treatment of hypertension. *Blood Press*. 1998;7:31–37.
44. Mimran A, Ruilope L, Kerwin L, et al. A randomized, double-blind comparison of the angiotensin II receptor antagonist, irbesartan, with the full dose range of enalapril for the treatment of mild-to-moderate hypertension. *J Hum Hypertens*. 1998;12:203–208.
45. Kassler-Taub K, Littlejohn T, Elliott W, et al. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan in mild-to-moderate hypertension. *Irbesartan Losartan Study Investigators. Am J Hypertens*. 1998;11:445–453.
46. Littlejohn T III, Saini R, Kassler-Taub K, et al. Long-term safety and antihypertensive efficacy of irbesartan: pooled results of five open-label studies. *Clin Exp Hypertens*. 1999;21:1273–1295.
47. Dahlof B, Devereux RB, Kjeldsen SE, et al. et al for the LIFE study group: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
48. Thurmann PA, Kenedi P, Schmidt A, et al. Influence of the Angiotensin II Antagonist Valsartan on Left Ventricular Hypertrophy in Patients With Essential Hypertension. *Circulation*. 1998;98:2037–2042.
49. Thurmann PA. Angiotensin II antagonism and the heart: valsartan in left ventricular hypertrophy. *J Cardiovasc Pharmacol*. 1999;33: S33–S36.
50. Martina B, Dieterle T, Weinbacher M, et al. Effects of losartan titrated to Losartan/Hydrochlorothiazide and amlodipine on left ventricular mass in patients with mild-to-moderate hypertension. A double-blind randomized controlled study. *Cardiology*. 1999;92:110–114.
51. Malmqvist K, Kahan T, Edner M, et al. Regression of left ventricular hypertrophy in human hypertension with irbesartan. *J Hypertens*. 2001; 19:1167–1176.
52. Dahlof B. Left ventricular hypertrophy and angiotensin II antagonists. *Am J Hypertens*. 2001;14:174–182.