Effects of Valsartan Treatment on Indicators of Cardiovascular Damage in Newly Diagnosed Hypertensive Patients: A Prospective, Twelve-Month, Open-Label, Pilot Study

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ABSTRACT

BACKGROUND: Myocardial fibrosis and dysfunction can be detected in the early phases of organ damage associated with hypertension. Valsartan, an angiotensin-II receptor blocker, is efficacious in lowering blood pressure (BP) and reducing left ventricular mass in patients with hypertension. Levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and procollagen type I carboxy-terminal propeptide (PICP) are correlated with organ damage in patients with overt congestive heart failure; however, few data are available in patients with hypertension.

OBJECTIVE: The aim of this study was to assess the effects of 12 months of valsartan treatment on echocardiographic measures and indices of organ damage (NT-proBNP and PICP) in newly diagnosed patients with hypertension.

METHODS: This was a prospective, open-label, single-center, exploratory study. Patients with newly diagnosed, previously untreated hypertension were treated for 12 months with valsartan 160 mg/d and compared with an equal number of healthy, untreated control subjects. Baseline and follow-up visits at 3, 6, and 12 months included physical examination, systolic BP (SBP) and diastolic BP (DBP) measurements, ECG, echocardiography, and NT-proBNP and PICP determination.

RESULTS: A total of 20 patients (mean [SD] age, 48.05 [7.29] years) were enrolled and compared with 20 healthy controls (age, 49.6 [6.95] years). Compared with baseline, valsartan was associated with reduced BP in the group with hypertension after 12 months of treatment (mean SBP, 150.05 [11.15] vs 120.00 [8.43] mm Hg, $P < 0.001$; DBP, 97.80 [8.36] vs 79.50 [4.26] mm Hg, $P < 0.001$). Compared with the control group, at baseline, the group with hypertension had significantly higher mean left ventricular mass index (LVMI) (119.88 [22.86] vs 87.31 [15.77] g/m²; $P < 0.001$), relative wall thickness (thickness/radius [h/r] ratio: 0.45 [0.08] vs 0.35 [0.07]; $P = 0.001$), and NT-proBNP (50.00 [32.01] vs 25.47 [9.69] pg/dL; $P = 0.002$). PICP

was higher, but the difference was not statistically significant (46.10 [15.69] vs 37.50 [7.20] µg/L). After 12 months, treatment with valsartan was associated with significant reductions in all measured parameters compared with baseline (LVMI, 106.51 [17.12] g/m^2, P = 0.004; h/r, 0.41 [0.07], P = 0.026; NT-proBNP, 22.55 [13.52] pg/dL, P = 0.001; PICP, 35.20 [9.19] µg/L, P < 0.008). At 12 months, patients with hypertension treated with valsartan achieved NT-proBNP and PICP levels not statistically different from those of the healthy controls (NT-proBNP, 22.55 [13.52] vs 25.24 [8.43] pg/dL; PICP, 35.20 [9.19] vs 36.90 [6.41] µg/L).

CONCLUSION: Patients treated with valsartan for 12 months had significant reductions in BP, LVMI, and indices of subclinical organ damage (NT-proBNP and PICP) compared with baseline. (*Curr Ther Res Clin Exp.* 2010;71:309–321) © 2010 Elsevier HS Journals, Inc.

KEY WORDS: hypertension, organ damage, angiotensin-II receptor blocker, valsartan, N-terminal pro-brain natriuretic peptide, procollagen type I carboxy-terminal propeptide.

INTRODUCTION

Hypertension is a major cardiovascular (CV) risk factor, and essential hypertension is considered an early stage in the continuum of CV disease, which progresses from atherosclerosis to fatal or nonfatal events.[1] Long-standing hypertension is associated with well-known modifications in heart structure and function, commonly represented by left ventricular hypertrophy (LVH) and left ventricular systolic and diastolic dysfunction (LVSDd). Echocardiography is deemed the gold standard for the detection of LVSDd preceding overt heart failure.[2,3]

The natriuretic peptide (NP) family plays a key role in blood pressure (BP) regulation through its direct vasodilator, diuretic, and natriuretic properties.[4] The NP family includes atrial NP (ANP) and brain NP (BNP), as well as the N-terminal (NT) fragments of their biosynthetic precursors (NT-proANP and NT-proBNP). BNP and NT-proBNP have been identified as simple tools to facilitate identification of LVH and LVSDd.[5] Plasma concentrations of cardiac-derived NPs have been associated with cardiac function and are considered hallmarks of congestive heart failure.[6] BNP, in particular, is a sensitive and very early indicator of ventricular wall stress,[7] and studies have suggested that the N-terminal fragment of the molecule is "at least equivalent" to BNP for the detection of LVSDd.[7,8]

There is increasing evidence that subclinical target organ damage occurs also in the early phases of the natural history of hypertension.[9–11] One common early event in the development of heart damage associated with hypertension is LVH, which can result from myocyte hypertrophy and interstitial accumulation of fibrous tissue.[12]

In patients with hypertension, myocardial fibrosis has a direct negative effect on clinical outcomes, because a higher collagen content increases myocardial stiffness, promotes cardiac dysfunction, and induces abnormalities of electrical activity and intramyocardial perfusion.[13] This suggests that the quantity and quality of cardiac tissue are responsible for CV events in these patients.[14] During the synthesis of collagen

type I, procollagen type I carboxy-terminal propeptide (PICP) is formed and released into the blood, and high serum concentrations of PICP can be found in cardiac fibrosis.[15] Therefore, serum levels of PICP have been proposed as a good marker of collagen type I synthesis and severe myocardial fibrosis.[16,17] In fact, circulating biomarkers of collagen turnover are currently known to provide a useful tool for the assessment of cardiac remodeling in patients with congestive heart failure and LVSDd after acute myocardial infarction.[18] Moreover, it has been found that serum PICP is higher in any setting of hypertensive heart disease than in normotensive controls.

Lowering BP is critical to reducing the CV complications of hypertension[19]; however, hemodynamic and nonhemodynamic factors play synergistic roles in myocardial fibrosis.[20]

Chronic pressure overload stimulates excessive collagen deposition. However, other biological variables may contribute to this process because the ability of antihypertensive treatment to reduce BP does not predict the extent of myocardial fibrosis regression.[21] Therefore, it seems reasonable that optimal treatment of arterial hypertension might favor the decrease of both cardiac mass and fibrosis. Preliminary evidence suggests that not all antihypertensive agents affect fibrosis to the same extent. Drugs that directly block the renin-angiotensin system (angiotensin-converting enzyme [ACE] inhibitors and angiotensin II receptor blockers [ARBs]) appear to be particularly efficacious in contrast to β-blockers and diuretics.[5] ARBs have been found to be as efficacious as ACE inhibitors in the management of hypertension, congestive heart failure, and chronic renal failure.[22] Several studies have reported that the ARB valsartan is not only an efficacious antihypertensive drug, but also is able to reduce left ventricular mass (LVM) and myocardial dysfunction and fibrosis.[22,23]

The present study was conducted to assess the effects of treatment with valsartan on both echocardiography parameters and circulating indices of heart damage (ie, NT-proBNP and PICP), in a population with newly diagnosed, previously untreated hypertension.

SUBJECTS AND METHODS

The study was approved by the local ethical committee at the University of Milan, Milan, Italy. All subjects were adequately informed of the nature of this clinical trial, and gave written informed consent prior to their participation. The study was conducted in accordance with the second amendment to the Declaration of Helsinki.

PARTICIPANTS AND PROCEDURES

A 12-month, open-label, single-center, exploratory study was conducted on men and women aged ≥18 years. Consecutive, nonselected patients with newly diagnosed, previously untreated arterial hypertension, who were referred to the authors' clinic for evaluation and treatment of the disease, were included in the hypertension group. *Hypertension* was defined by repeatedly documented systolic BP (SBP) >139 mm Hg and diastolic BP (DBP) >89 mm Hg. The presence of a hypertensive condition secondary to renal disorders, renal artery abnormalities, adrenocortical disorders, pheochromocytoma, and iatrogenic causes was systematically excluded by analysis of blood

samples and clinical evaluations, and echography of the upper abdomen in suspected nephrovascular hypertension. Patients in the hypertensive group received valsartan 160 mg/d orally in the morning, during the entire 12-month study period. Valsartan had to have been their first antihypertensive treatment, and concomitant antihypertensive medications were not allowed during the observation period.

The control group included healthy, normotensive, adult subjects of both sexes who had been referred to the center and determined to be normal. Healthy volunteers were recruited from the volunteer database at the center and evaluated in the same manner. This group received no antihypertensive treatment.

Study visits were performed at baseline and then at 3, 6, and 12 months. At each visit, every participant underwent a complete physical examination, BP measurement, venous blood sample collection, ECG, and echocardiographic examination. SBP and DBP were measured in the sitting position after 5 minutes of rest, using a conventional sphygmomanometer with an appropriately sized cuff on the left upper arm. After overnight fasting, venous blood samples were drawn for both routine laboratory tests (including glucose, creatinine, and urea nitrogen), and determination of NT-proBNP and PICP. Blood samples for the measurement of plasma NT-proBNP and PICP concentrations were collected in 7-mL disodium-EDTA–containing test tubes, and immediately centrifuged at 3000 rpm for 10 minutes. Plasma samples from each patient were stored in 2 separate 1-mL vials until they were analyzed by an investigator (G.B.B.) who was blinded to the study group designation. Plasma levels of NT-proBNP were measured by an electrochemiluminescent immunoassay (Elecsys, Roche Diagnostics, Mannheim, Germany), whereas PICP levels were determined by a commercially available radioimmunoassay (Procollagen PICP RIA Kit, Orion Diagnostics, Espoo, Finland).

Two-dimensional echocardiography and targeted M-mode recording were obtained in each patient as recommended. Echocardiography was performed (Sonoline G50, Siemens AG, Erlangen, Germany) with a 2.5- or 3.5-MHz probe. Images were obtained from the parasternal and apical windows, with the patient lying on his or her left side. All of the recordings were performed at the end of expiration, to get the best quality images. LVM was calculated by the Devereux formula[24]:

$$LVM = 1.04 \times [(LVIDd + IVSd + PWTd)3 - LVIDd3] - 13.6,$$

where *LVIDd* was the left ventricular end-diastolic internal diameter, *IVSd* was the end-diastolic interventricular septum thickness, and *PWTd* was the left ventricular end-diastolic posterior wall thickness. LVM index (LVMI) was calculated by dividing the LVM by body surface area. Left ventricular thickness/radius (h/r) ratio was calculated by dividing the sum of IVSd and PWTd by LVIDd (normal value <0.45). All measurements were carried out by an echocardiographer (B.C. or G.R.) blinded to treatment groups.

STATISTICAL ANALYSIS

Continuous variables (SBP, DBP, LVMI, h/r, NT-proBNP, and PICP) were expressed in terms of mean (SD). Comparisons between groups for BP and biomarker

values were performed by t test for independent groups. In each group, changes from baseline to 12 months in BP values and biomarker concentrations were analyzed by paired t test. ProBNP and PICP values usually have a skewed distribution; therefore, they were log-transformed before t test analyses. Differences in gender distribution between the hypertension and control groups were assessed by Fisher exact test. The level of significance was fixed at 0.05 for 2-sided tests. The Bonferroni correction was adopted to assess significance in multiple comparisons. According to this criterion, to maintain the family-wise error rate (that is, the significance level for the whole family of tests) at 0.05, each of the individual k tests carried out on each parameter was judged significant if the observed P value was <0.05/k.

All statistical analyses were performed using SAS software version 8.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Thirty-five hypertensive patients were approached for enrollment, 15 of whom were excluded from the study (8 for secondary hypertension, 5 for refusal of consent, and 2 for having "white coat" hypertension). Therefore, the study population included 20 patients in the hypertension group (7 females and 13 males; mean [SD] age, 48.05 [7.29] years [range, 36–62 years]) and 20 controls (10 females and 10 males; age, 49.6 [6.95] years [range, 38–58 years]). Data were available from all 40 enrolled subjects; all participants in both groups completed the study and were included in the effectiveness analysis. Hypertension and healthy control groups were not significantly different in terms of age or sex.

BLOOD PRESSURE CONTROL

At baseline, mean (SD) SBP was 150.05 (11.15) mm Hg and DBP was 97.80 (8.36) mm Hg in the hypertension group, compared with 116.50 (10.27) mm Hg and 79.50 (4.84) mm Hg, respectively, in the control group. The difference between the hypertension group and the control group was statistically significant for both SBP and DBP (both, $P < 0.001$).

Treatment with valsartan 160 mg/d was associated with reduced BP values in patients with hypertension, allowing them to reach recommended therapeutic goals (**Figure 1**). After 12 months of treatment, mean (SD) SBP and DBP values in the hypertension group were 120.00 (8.43) mm Hg and 79.50 (4.26) mm Hg, respectively (both, $P < 0.001$ vs baseline). There were no significant differences between BP measurements at baseline and those at 12 months in the control group.

ECHOCARDIOGRAPHIC PARAMETERS

Figure 2 shows LVMI and h/r values at baseline and 12 months in both study groups. At baseline, mean (SD) LVMI was significantly higher in hypertensive patients (119.88 [22.86] g/m^2) compared with healthy controls (87.31 [15.77] g/m^2; $P < 0.001$). Similarly, the h/r ratio was significantly higher in the hypertensive group (0.45 [0.08]) compared with the control group (0.35 [0.07]; $P < 0.001$).

In the hypertensive group, after 12 months of treatment with valsartan, mean (SD) LVMI was significantly improved compared with baseline (106.51 [17.12] g/m^2; change
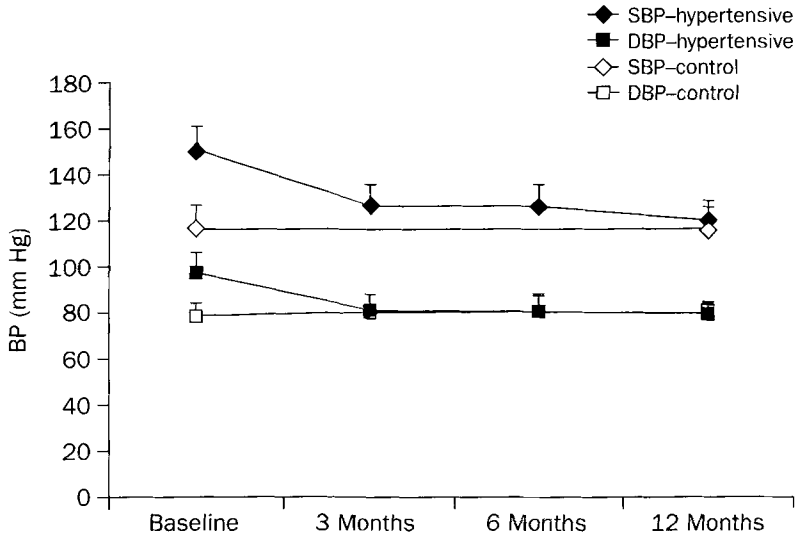
Figure 1. Mean (SD) systolic blood pressure (SBP) and diastolic BP (DBP) in the hypertensive group (at baseline and at 3, 6, and 12 months of valsartan treatment) and in the healthy control group (at baseline and at 12 months).

from baseline, -13.17 [20.44]; $P = 0.004$). Values for h/r ratio at 12 months showed an improvement compared with baseline (0.41 [0.07]; change from baseline, -0.04 [0.08]; $P = 0.026$), although the difference lacked statistical significance according to the Bonferroni correction. The results at 12 months in the control group were virtually unchanged compared with baseline (LVMI baseline, 87.31 [15.77] g/m^2 vs 12 months, 82.96 [18.88] g/m^2; h/r baseline, 0.35 [0.07] vs 12 months, 0.34 [0.08]). Between-group differences in LVMI and h/r values at 12 months were lower compared with baseline, but still remained significant after 12 months ($P < 0.001$ for LVMI and $P < 0.005$ for h/r).

MARKERS OF ORGAN DAMAGE

Figure 3 shows the NT-proBNP and PICP values at baseline and 12 months in both study groups. At baseline, mean (SD) NT-proBNP levels were significantly higher in hypertensive patients (50.00 [32.01] pg/dL) compared with healthy controls (25.47 [9.69] pg/dL; $P = 0.002$ after log-transformation). PICP levels were numerically higher in the hypertension group (46.10 [15.69] μg/L) compared with the control group (37.50 [7.20] μg/L), but this difference was not statistically significant.

In the hypertension group, after 12 months of treatment with valsartan, mean (SD) NT-proBNP levels significantly improved compared with baseline (22.55 [13.52] pg/dL; change from baseline, -27.45 [30.88] pg/dL; $P < 0.002$ after log-transformation). PICP levels were also significantly lower compared with baseline (35.20 [9.19] μg/L; change from baseline, -10.90 [14.31] μg/L; $P < 0.008$ after log-transformation). Similarly to LVMI and h/r ratios, the results at 12 months for NT-proBNP and PICP in
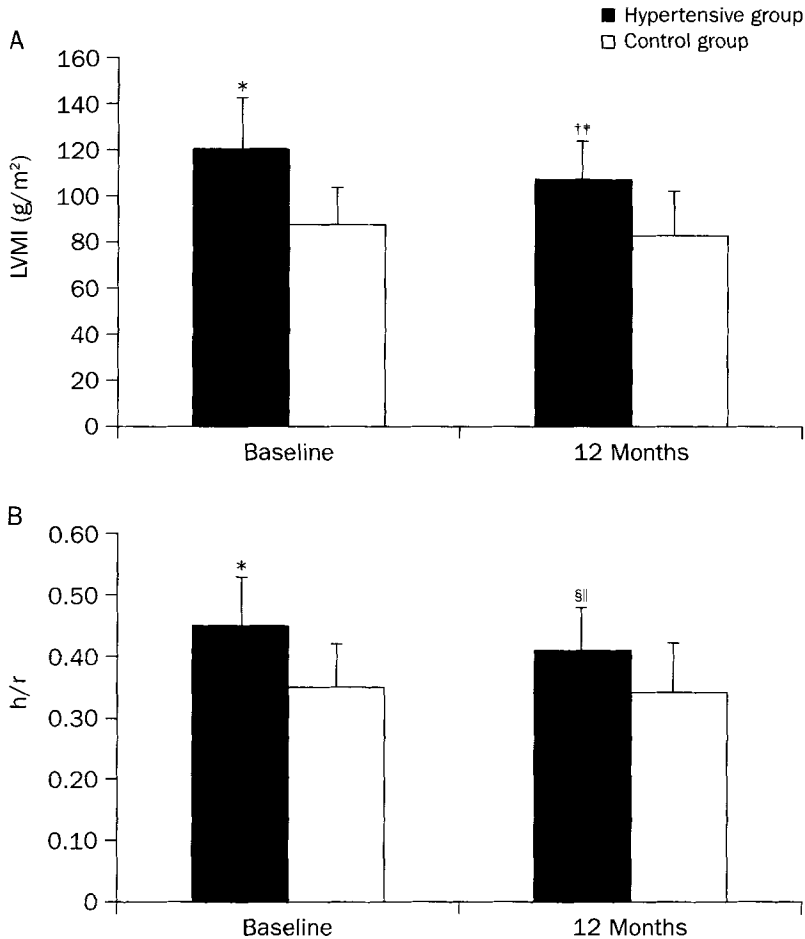
Figure 2. Mean (SD) (A) left ventricular mass index (LVMI) and (B) left ventricular thickness/ radius (h/r) ratio values at baseline and at 12 months in the hypertensive and healthy control groups. *P < 0.001 versus the control group; †P = 0.001 versus the control group; ‡P = 0.004 versus baseline; §P < 0.005 versus the control group; ‖P = 0.026 versus baseline.

the control group were virtually unchanged compared with baseline (NT-proBNP baseline, 25.47 [9.69] pg/dL vs 12 months, 25.24 [8.43] pg/dL; PICP baseline, 37.50 [7.20] µg/L vs 12 months, 36.90 [6.41] µg/L). Therefore, after 12 months of valsartan treatment, NT-proBNP and PICP levels in patients with hypertension were not statistically different from those of healthy controls.

DISCUSSION

Twelve months of monotherapy with valsartan 160 mg/d was associated with significantly reduced BP values to recommended targets (< 140/90 mm Hg) in all patients
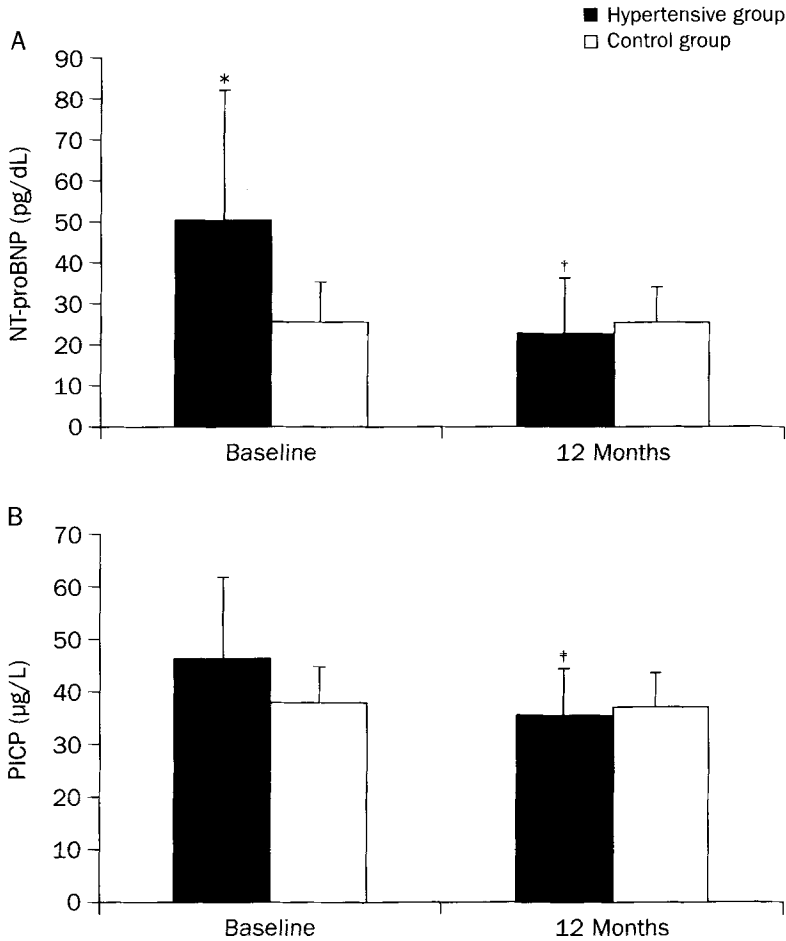
Figure 3. Mean (SD) (A) N-terminal pro-brain natriuretic peptide (NT-proBNP) and (B) pro-collagen type I carboxy-terminal propeptide (PICP) values at baseline and at 12 months in the hypertensive and healthy control groups. *P = 0.002 versus the control group; †P = 0.002 versus baseline; ‡P < 0.008 versus baseline.

with newly diagnosed, previously untreated hypertension enrolled in the present study. This finding is consistent with the results of several large studies on valsartan, such as the VALUE trial[25] and the recent PREVIEW study.[26] The Canadian Valsartan Observational Study (DIOVANTAGE 4)[27] included 34,033 patients with essential hypertension treated with valsartan (alone or in combination with hydrochlorothiazide), 38% of whom were newly diagnosed with hypertension. This trial confirmed the benefits of single-drug treatment with valsartan 80 or 160 mg/d for controlling BP, along with good safety and tolerability profiles. Furthermore, monotherapy with an ARB such as valsartan is among the regimens recommended by European guidelines to adequately lower BP and improve cardiovascular outcomes.[28]

In the present study, the satisfactory BP control obtained during the entire follow-up period is in accordance with the significant improvements observed in echocardiographic parameters, although both LVMI and h/r ratios remained higher in hypertensive subjects than in normotensive subjects after 12 months. This finding may be related to the time lag between the onset of successful antihypertensive treatment and achievement of full regression of these morphologic changes. On the contrary, hypertensive patients had significantly higher NT-proBNP and PICP values at baseline compared with the healthy controls, and these differences were not statistically significant at study end point. Although the results come from a small group of patients, the reliability of these findings is supported by the stability of both indices after 12 months in normotensive subjects lacking other causes of heart damage. And, although both baseline NT-proBNP and PICP concentrations in the hypertensive group were within the reported normal ranges[13,29] for subjects with normal heart function, there were significant decreases in their values after 12 months of valsartan treatment, consistent with regression of subclinical organ damage.

The data presented here, in accordance with those in the literature, suggest a potential beneficial action of valsartan beyond just the reduction of BP, in the early phase of hypertensive disease.[30] In fact, the early changes in organ damage markers should not—or at least should not completely—be ascribed to the extent of BP reduction. Evidence from experimental models indicates that not all antihypertensive agents have antifibrotic effects and cardiovascular tissue specificity.[31] In small studies based on cardiac biopsies in humans, treatment with different antihypertensive drugs was associated with varying degrees of myocardial fibrosis regression. Furthermore, it was reported that the ability of antihypertensive treatment to reduce BP did not predict its capacity to reverse myocardial fibrosis.[14]

Agents directly blocking the renin–angiotensin system appear to be particularly active in promoting regression of fibrosis, in contrast to β-blockers and diuretics. In fact, angiotensin II induces vasoconstriction, cell proliferation, and collagen synthesis, contributing to the development of hypertrophy, myocardial fibrosis, and cardiac remodelling.[32] A large body of evidence supports a major role for angiotensin II as a critical factor responsible for both fibroblast proliferation and alteration of fibrillar collagen turnover, which in turn lead to increased myocardial stiffness and promote diastolic and systolic dysfunction, electrical activity abnormalities, and impaired intramyocardial perfusion.[13] In this context, the ACE-inhibitor lisinopril was associated with significantly less cardiac fibrosis than hydrochlorothiazide in a small series of hypertensive patients enrolled in a double-blind, randomized trial.[33] In the LVH Regression with the Angiotensin Antagonist Losartan (REGAAL) study, which included 225 patients, the ARB losartan reduced both LVMI and BNP compared with the β-blocker atenolol.[34] Moreover, losartan, but not the calcium channel blocker amlodipine, was associated with a decrease in collagen volume fraction and PICP values in hypertensive patients,[35] leading the authors to suggest that PICP levels might be used to determine treatment effectiveness on myocardial fibrosis. Diez et al[36] also found that losartan treatment was associated with a decrease in PICP levels, but only in patients with severe myocardial fibrosis.[16]

In the present study, patients with newly diagnosed arterial hypertension and sub-clinical organ damage were treated with valsartan for 12 months, showing a favorable effect of the drug in this population. The findings are consistent with data from the large Valsartan Heart Failure Trial,[37] in which baseline BNP values were recorded in 4284 patients with symptomatic chronic heart failure randomly assigned to valsartan or placebo as add-on to standard treatment. In the valsartan group, plasma BNP levels showed a significant reduction after 4, 12, and 24 months of follow-up. In the placebo group, plasma BNP concentrations progressively increased ($P < 0.001$ in all comparisons vs placebo, at each time point). Furthermore, the benefit of valsartan on BNP levels in that trial was also observed in patients already treated with an ACE inhibitor and a β-blocker, and was consistent with an improvement of left ventricular function, although this latter observation did not affect mortality rates.

It should be noted that this study was not designed to investigate whether valsartan is more efficacious than diuretics or β-blockers in reducing the outcomes measured. As of the writing of this article, there is no study in the literature indicating that β-blockers or diuretics reduce PICP, because these drugs, in effect, lack any direct action on collagen and procollagen. Therefore, while this analysis cannot definitively suggest that the outcomes were due to valsartan in particular, and although it is possible that the results came from BP reduction alone, it seems that valsartan exerted a major effect on the measured parameters. BP control may be an additional favorable factor especially regarding the BNP decrease; however, the effect of ARBs on PICP is evident. A study including a control group receiving a different antihypertensive treatment might help to clarify this point.

Limitations of the present study include its small sample size, though it was in-tended to be exploratory in nature. For this reason, it was not possible to analyze the severity of hypertension at baseline, or correlate it with circulating indices of subclini-cal organ damage or with the effects of 1-year valsartan administration on their levels. However, the between-group differences in NT-proBNP and PICP concentrations at baseline were clearly evident, as was their disappearance after 1 year of treatment.

While levels of NT-proBNP are known to be higher in women than in men,[38] and this study enrolled 10 women and 10 men in the control group compared with 7 women and 13 men in the hypertension group, higher levels of this marker were found in the patients with hypertension than in the control group at baseline. There was no statis-tical difference between groups after 12 months of follow-up. In addition, the results were supported by the coherence of changes in NT-proBNP and PICP over time, as the patients of this study were not affected by other conditions known to be associated with altered PICP, such as renal impairment, coronary artery disease, hepatic dysfunc-tion, pulmonary fibrosis, or metabolic bone disease.

The clinical relevance of these findings stems from recommendations in the guide-lines from the European Society of Hypertension,[28] underscoring the importance of preventing organ damage due to hypertension in an early phase of the disease. Valsar-tan is the first drug found to have effects on such an important marker as PICP. In this perspective, it is also important to note that mortality has not been shown to be dif-ferent with the use of valsartan over other drugs.

CONCLUSIONS

In this study, patients treated with valsartan for 12 months had significant reductions in BP, LVMI, and indices of subclinical organ damage (NT-proBNP and PICP) compared with baseline. Furthermore, the significant decrease of NT-proBNP and PICP, indices of early heart dysfunction and fibrosis, suggests that further investigations are warranted to evaluate the potential effects of valsartan on the prevention or delay of target organ damage.

ACKNOWLEDGMENTS

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