

Efficacy and Tolerability of the Combination Valsartan/Hydrochlorothiazide Compared with Amlodipine in a Mild-to-moderately Hypertensive Brazilian Population

ROBERTO J.S. FRANCO¹, SUELY GOLDFLUS², MARI MCQUITTY³ AND WILLE OIGMAN⁴ ON BEHALF OF THE VALSARTAN/HCTZ COMBINATION THERAPY IN BRAZIL STUDY GROUP

From the ¹Botucatu Medical School, Department of Medicine, Nephrology Division, São Paulo, Brazil; ²Novartis Biociências SA, São Paulo, Brazil; ³Novartis Pharma AG, Basel, Switzerland; ⁴Clínica Médica da Universidade Estadual do Rio de Janeiro, Rio de Janeiro, Brazil

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Most hypertensive patients need more than one drug to reach recommended blood-pressure targets. We investigated the effects on 24-h ambulatory blood pressure (ABP) of the angiotensin-receptor blocker, valsartan, in combination with hydrochlorothiazide (HCTZ), compared with the calcium-channel blocker amlodipine in a Brazilian population in a multicentre, double-blind, double-dummy, parallel group, controlled study in 373 patients with essential hypertension. After a 2-week washout period, patients with a mean sitting systolic blood pressure (SBP) of 160–190 mmHg were randomized to receive either valsartan 160 mg o.d., or amlodipine 5 mg o.d. for 2 weeks and subsequently force-titrated to valsartan 160 mg/HCTZ 25 mg o.d. or amlodipine 10 mg o.d. This regimen was continued until the end of the study at week 8. The primary efficacy parameter was the change from baseline to week 8 in mean 24-h SBP. Secondary endpoints were change in mean 24-h diastolic blood pressure (DBP), tolerability and safety of treatments. Valsartan/HCTZ achieved a mean reduction in systolic ABP of -19.1 ± 11.3 mmHg compared with -20.7 ± 12.0 mmHg with amlodipine ($p = 0.324$ for the comparison) and in diastolic ABP by -11.1 ± 7.4 mmHg vs -11.6 ± 7.2 mmHg by amlodipine ($p = 0.853$ for the comparison). The valsartan/HCTZ group exhibited markedly lower rates of adverse events and discontinuations than the amlodipine group. Peripheral oedemas were far more frequent with amlodipine than with valsartan/HCTZ (1.6% with valsartan/HCTZ; 16.8% with amlodipine). Thus, the valsartan 160 mg/HCTZ 25 mg combination appears to be as efficacious as amlodipine 10 mg in this patient population but better tolerated. *Key words:* angiotensin-receptor blocker, calcium-channel blocker, combination therapy, ethnicity, hypertension.

INTRODUCTION

Pharmacological treatment of hypertension has among the most well-documented preventive effects in medicine. Evidence from prospective, randomized clinical trials in close to 50000 individuals supports the reduction in risk of cardiovascular events and all-cause mortality with appropriate reduction of blood pressure (BP) [1]. Current recommendations from the World Health Organization–International Society of Hypertension (WHO-ISH) [2] define optimal BP as $<120/80$ mmHg and normal BP as $<130/85$ mmHg. The latest recommendations from the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII), sets the limit for normal BP at $<120/80$ mmHg and defines patients with BP 120/80–139/89 mmHg as “pre-hypertensive” [3].

The widespread awareness of the risks from elevated BP is reflected in the fact that hypertension is one of the leading indications for drug prescriptions [4]. Paradoxically, however, this awareness is not reflected in control rates. Less than 30% of hypertensive patients reach treatment targets [5–7]. One reason for this is that monotherapy is frequently insufficient to reach target BP levels and the majority of hypertensive individuals need a combination regimen of several medications [8]. This has been recognized in the latest guidelines, which recommend combination treatment in all patients more than 20/10 mmHg above target [3]. Another reason for low control rates is low compliance rates with anti-hypertensive pharmacotherapy [9].

A logical treatment strategy is to block the renin–angiotensin system (RAS) in combination with a low dose of a diuretic. This is common with the newer class of

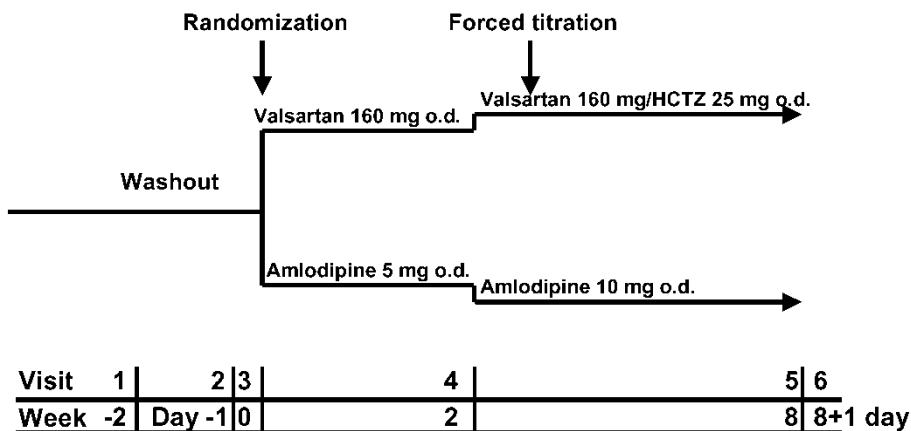


Fig. 1. Study design.

RAS-modulating drugs, the angiotensin-receptor blockers (ARBs), which have the benefit of being well tolerated in clinical practice. Hypertensive patients on ARBs have the highest compliance rates among treated hypertensives [10].

To gather more information on the effects of combination therapy vs established monotherapies, we investigated the effects on 24-h ambulatory BP (ABP) of the orally active ARB, valsartan, in combination with the diuretic, hydrochlorothiazide (HCTZ), compared with the calcium-channel blocker (CCB), amlodipine, in a Brazilian population. In recent years, the mean doses of ARBs used in therapy have tended to increase, as awareness has increased of the tolerability, low risk and possible benefits beyond BP reduction from treatment with ARBs at higher doses [11–13], e.g. valsartan has been used in heart failure and hypertension at up to 320 mg/day. To reflect this emerging paradigm, we used 160 mg o.d. of valsartan and 25 mg o.d. HCTZ. The efficacy and tolerability of valsartan 160 mg in combination with HCTZ have been demonstrated by earlier studies [14–15] and the combination has also been shown to reduce pulse pressure in a European population [16], but none of these studies compared the combination with active treatment with a CCB.

METHODS

Patients

Patients were recruited at 20 Brazilian centres. The study enrolled male and female outpatients, 21–70 years old, with mild-to-moderate hypertension (mean sitting systolic BP [MSSBP] $\geq 160 < 190$ mmHg if not treated and ≥ 140 mmHg if on antihypertensive medication). Patients with severe hypertension (DBP ≥ 110 mmHg and/or SBP ≥ 190 mmHg) were excluded from the study, as were obese (body mass index > 35 kg/m²) patients. Patients were further excluded if they had heart failure or a history of heart failure or myocardial infarction within the

preceding 12 months or if they were diabetic. Patients with serum potassium levels ≥ 5.5 mmol/l or ≤ 3.5 mmol/l were also excluded, as were patients unable to discontinue previous antihypertensive medication during the washout phase, and patients receiving concomitant antihypertensive treatment.

The study was conducted in accordance with good clinical practice and the current revision of the Declaration of Helsinki [17]. All patients gave written informed consent to take part. The study protocol and written subject information were reviewed and approved by the Ethics Review Committees for each site.

Study design

This was a multicentre, double-blind, double-dummy, parallel group, controlled study in 373 patients with essential hypertension. The primary objective was to demonstrate superior antihypertensive efficacy of valsartan/HCTZ 160/25 mg o.d. over amlodipine 10 mg o.d. The primary efficacy parameter was change from baseline to week 8 in mean 24-h SBP obtained by ABP monitoring. Secondary endpoints were change in mean 24-h DBP, tolerability and safety of treatments.

The study design is shown in Fig. 1. After a 2-week washout period, patients with an MSSBP of $\geq 160 < 190$ mmHg were randomized to receive either valsartan 160 mg o.d. or amlodipine 5 mg o.d. for 2 weeks. Subsequently, patients were force-titrated to valsartan 160 mg/HCTZ 25 mg o.d. or amlodipine 10 mg o.d. This regimen was continued until the end of the study at week 8. All medications were taken in the morning.

Ambulatory BP measurements were performed at week 0 (starting 24 h prior to visit 3) and week 8 (starting at visit 5, 24 h prior to visit 6). BP was measured with an oscillometric Spacelabs equipment (Spacelabs, Redmond, Washington, USA). The quality of each measurement was monitored to ensure 25 h of BP recordings with 70% or greater successful measures and ≥ 50 valid measurements

Table I. Baseline characteristics (ITT population)

Variable	Valsartan/HCTZ (n = 173)	Amlodipine (n = 170)	Total (n = 343)
Age years ± SD	54.7 ± 8.4	55.9 ± 9.0	55.3 ± 8.7
Sex, n (%)			
Male	44 (25.4%)	57 (33.5%)	101 (29.4%)
Female	129 (74.6%)	113 (66.5%)	242 (70.6%)
Race, n (%)			
Caucasian	70 (40.5%)	77 (45.3%)	147 (42.9%)
Black	37 (21.4%)	25 (14.7%)	62 (18.1%)
Oriental	3 (1.7%)	3 (1.8%)	6 (1.7%)
Other	63 (36.4%)	65 (38.2%)	128 (37.3%)
Hypercholesterolaemia, n (%)	21 (12.1%)	22 (12.9%)	43 (12.5%)
Hyperlipidaemia, n (%)	12 (6.9%)	9 (5.3%)	21 (6.1%)
Mean ± SD 24-h systolic ABP mmHg	149.9 ± 13.8	151.0 ± 12.8	150.5 ± 13.3
Mean ± SD 24-h diastolic ABP mmHg	92.8 ± 9.9	93.8 ± 9.2	93.3 ± 9.6

HCTZ, hydrochlorothiazide; SD, standard deviation; ABP, ambulatory blood pressure.

over the 24-h period. Measurements were averaged over hourly bases.

Safety

Safety was evaluated by recording adverse events (AEs) and serious AEs (SAEs) and by vital signs measures. At visits 2 and 6, biochemical safety profiles were evaluated, including glucose, potassium, total cholesterol, triglycer-

ides, uric acid, creatinine, sodium, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Statistical methods

The primary and secondary efficacy analyses were based on the intent-to-treat (ITT) population, which was defined as all patients with baseline and one post-baseline ABP measurement. The primary efficacy parameter was tested with an ANCOVA model, including baseline value as a

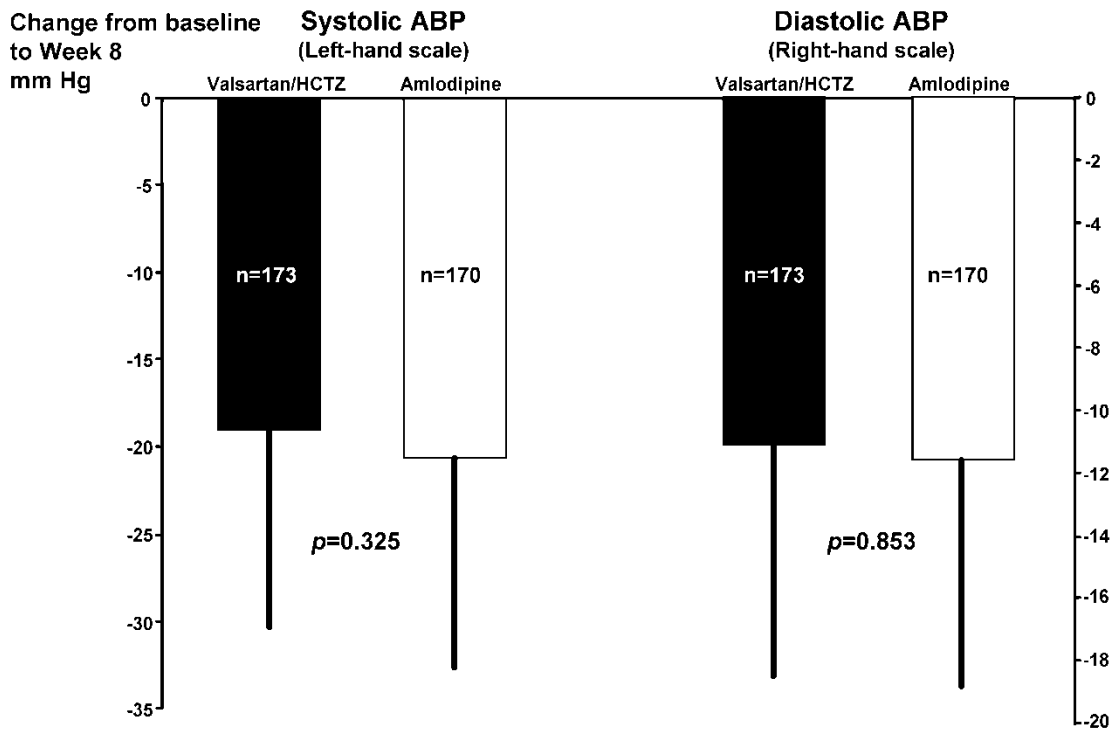


Fig. 2. Change from baseline to week 8 in mean 24-h ambulatory blood pressure (ABP) for the valsartan/hydrochlorothiazide (HCTZ) and amlodipine groups, respectively. The bars indicate standard deviation.

covariate and treatment and centre as factors. A two-sided significance level of 5% was used. For robustness purposes, a Wilcoxon rank-sum test was performed on the ITT population as an exploratory analysis. The safety population was used for all safety analyses.

For the sample size calculation, a difference between treatments of 3 mmHg was considered clinically relevant. To ensure a power of 80% to demonstrate such an effect with 9.2 mmHg standard deviation (SD) at the significance level of 5%, two-sided, based on a two-sample *t*-test, 149 evaluable patients per treatment group were needed. To account for a 15% dropout rate, it was estimated that 352 patients would need to be randomized.

RESULTS

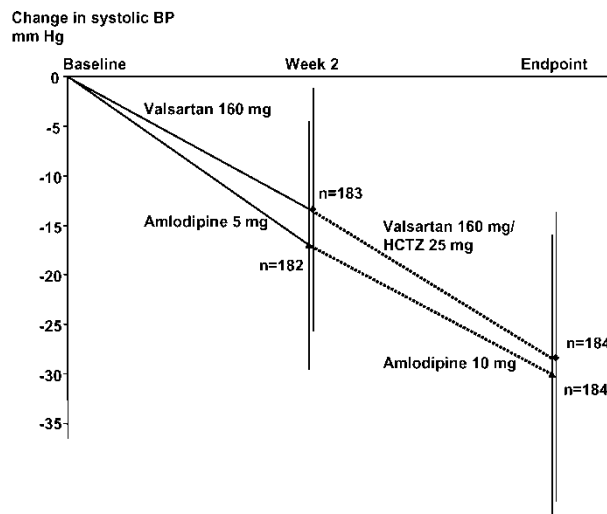
Baseline characteristics

After the 2-week washout period, a total of 370 patients were randomized to receive study treatment (185 to each study arm). Of these, 343 patients had one post-baseline ABP measurement and were included in the ITT population (173 in the valsartan/HCTZ arm and 170 in the amlodipine arm). Baseline characteristics are shown in Table I. The groups were balanced for age, metabolic disorders and ABP. There were more women in the valsartan/HCTZ group than in the amlodipine group and the valsartan/HCTZ group also had a greater number of black patients (21.4% vs 14.7%). The racial composition resembled that of the Brazilian population as a whole, with a high number of patients classified as "other".

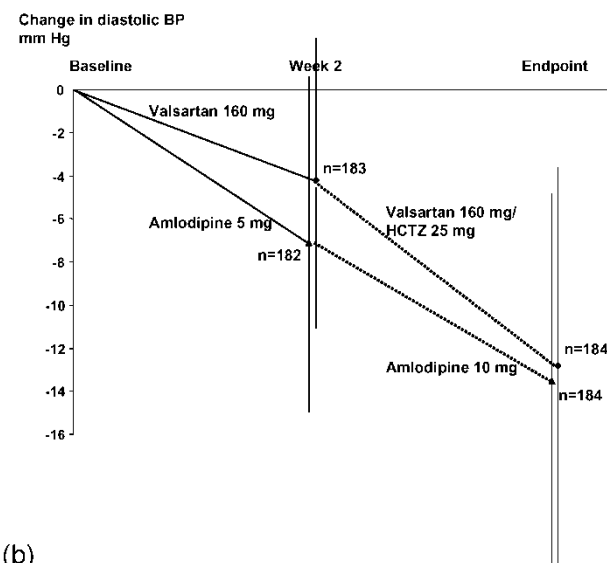
Efficacy

Both treatments significantly reduced ABP at week 8. As shown in Fig. 2, there were no statistically significant differences in overall BP-lowering efficacy between the two groups. Valsartan/HCTZ achieved a mean reduction in systolic ABP of -19.1 ± 11.3 mmHg compared with a reduction of -20.7 ± 12.0 mmHg with amlodipine ($p = 0.324$ for the comparison). For diastolic ABP, the reduction with valsartan/HCTZ was -11.1 ± 7.4 mmHg vs -11.6 ± 7.2 mmHg in the amlodipine group ($p = 0.853$ for the comparison). Hence, although the primary aim of proving superiority was not achieved, the overall efficacy of the valsartan 160 mg/HCTZ 25 mg combination seems to be as great as amlodipine 10 mg in this patient population.

The addition of 25 mg HCTZ to valsartan 160 mg seemed to have a greater effect on efficacy than doubling the amlodipine dose from 5 to 10 mg. Whereas amlodipine 5 mg tended to be more efficacious than valsartan 160 mg during the short (2-week) monotherapy phase (Fig. 3), this trend was reversed in the 6-week combination-therapy phase, where the additional BP reduction achieved with valsartan/HCTZ was greater than that achieved with amlodipine 10 mg. This effect was par-



(a)



(b)

Fig. 3. Change in office blood pressure (BP) during the monotherapy phase and the combination-therapy phase, respectively. Bars indicate standard deviation. (a) Changes in systolic BP; (b) changes in diastolic BP.

ticularly pronounced for diastolic BP, as shown in Fig. 3b. However, these assessments were not a predefined aim of the study, and hence, no definite conclusion can be drawn as to these differences.

On the variables diurnal systolic and diastolic load, there were no statistically significant differences between the treatment groups. The same lack of statistically significant superiority of one treatment over another was observed for smoothness index.

Safety

Both treatments were well tolerated but the valsartan/

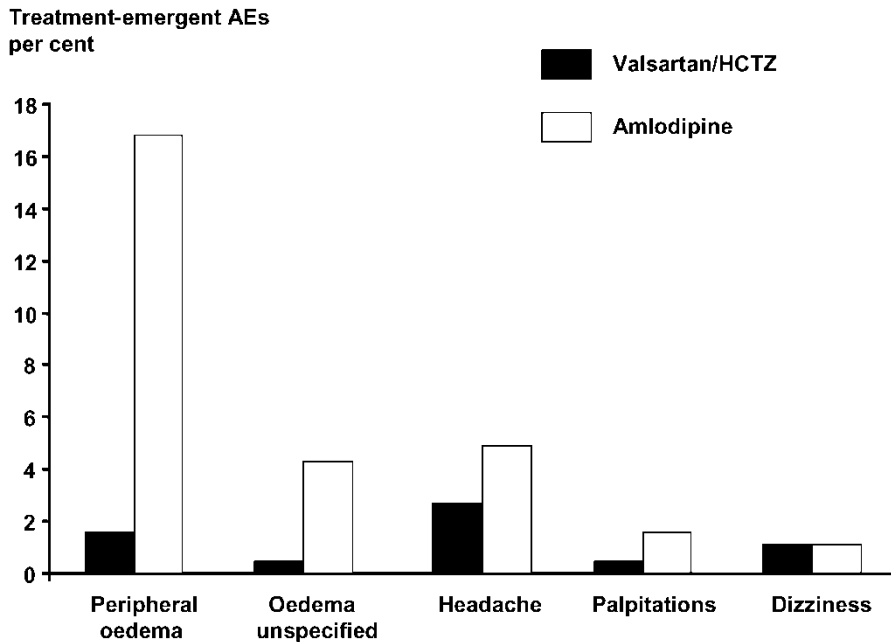


Fig. 4. Most frequent treatment-related adverse events (AEs).

HCTZ group exhibited markedly lower rates of AEs and discontinuations than the amlodipine group. Four patients (2.2%) discontinued the study because of AEs with valsartan/HCTZ compared with 13 patients (7.0%) with amlodipine. Rates of treatment-related AEs were similarly higher in the amlodipine group (Fig. 4). Seventeen suspected drug-related AEs (9.2%) were observed with valsartan/HCTZ and 51 (27.6%) with amlodipine. Peripheral oedemas were more frequent by an order of magnitude in the amlodipine group than in the valsartan/HCTZ group (1.6% with valsartan/HCTZ; 16.8% with amlodipine). Headache, the most frequent treatment-related AE with valsartan/HCTZ (2.7%) was more frequent still (4.9%) in the amlodipine group.

There were no changes in AST or ALT in either of the groups. Changes in serum creatinine were insignificant and did not differ markedly between groups (mean increase 0.04 mg/dl [5%] with valsartan/HCTZ; mean decrease -0.2 mg/dl [2%] with amlodipine).

DISCUSSION

This study shows that, over an 8-week period, the reduction in 24-h ABP with the combination valsartan 160 mg/HCTZ 25 mg is similar to that of with the CCB amlodipine 10 mg in a Brazilian population of patients with mild-to-moderate hypertension. There were no significant differences in efficacy for either systolic or diastolic ABP between the treatments ($p > 0.05$ for both comparisons). This indicates that, evaluated on crude BP-lowering efficacy alone, the two therapeutic options are exchangeable. However, if tolerability is taken into

account, the valsartan/HCTZ combination seems to have major advantages.

The differences in AE rates were predominantly in rates of peripheral oedemas, which are a well-known side-effect of CCBs [18]. It is notable that there were no increases in serum creatinine levels with valsartan/HCTZ, contrary to what is sometimes anticipated with ARB/diuretic combinations. These tolerability data further support the utility of such combinations and add weight to the argument that ARB/HCTZ regimens may show better compliance rates than what is seen with other powerful antihypertensive pharmacotherapies. In view of the increased emphasis on the role of combination treatments in optimal antihypertensive therapy [3], the positive results we report provide further support for this treatment option.

The basis of combination therapy is to target several mechanisms of BP control; e.g. blocking the angiotensin AT₁-receptor mediated sodium retention and vasoconstriction with an ARB and reducing volume with a diuretic. In recent years, there has been a growing awareness of possible benefits from ARBs at higher doses than those previously used as starting doses in hypertensive populations [19]. Since the side-effect profile of ARBs is very similar to placebo, this has led to an increased interest in the benefits from higher starting doses than originally recommended. The combination valsartan 160 mg/HCTZ 12.5–25 mg has previously been shown to be safe and effective [14–15], but the earlier studies have not compared the combination directly with CCBs or other treatment regimens. Although the primary superiority aim of the current study was not achieved, the

results support the efficacy and safety of valsartan/HCTZ in a wide range of patients, at a starting dose of 160 mg valsartan.

The failure to show superiority may be partly explained by the lower effect of valsartan compared with amlodipine 5 mg in the short (2 weeks) monotherapy part of the trial. The study population included a substantial number of black patients and this proportion was greater in the valsartan group than in the amlodipine group. Monotherapy with ARBs, as with ACE inhibitors or diuretics, is believed to be less effective in black populations than in Caucasians [8, 20]. However, adding HCTZ to AT₁-receptor blockade has been shown to have particularly strong effects in black patients [21–22]. For valsartan/HCTZ, this has been shown for in African-Americans, where valsartan 160 mg/HCTZ 12.5 mg appears to be one of the most effective regimens [21]. This synergy in black populations is probably responsible for the greater additional effects with valsartan/HCTZ than with amlodipine 10 mg between weeks 2 and 6. This additional BP reduction in the valsartan/HCTZ group was not powerful enough to achieve overall superiority at endpoint, but it can be hypothesized that a longer-lasting study would have been able to show such an outcome. A specifically designed trial would be needed to verify this speculation.

Moreover, the findings extend the conclusions of earlier studies with ARB/HCTZ combinations to cover a Brazilian population, which consists of a greater ethnic mixture than what is usually included in clinical trials with antihypertensive agents [23]. The population of Brazil has a high proportion of individuals classified as mixed-race (mainly black/white). It is unclear how individuals from such mixed ethnic backgrounds respond to antihypertensive treatments, but the results presented here indicate that combined ARB/diuretic therapy is as efficacious, and better tolerated than high-dose CCBs in this population. As oedema may often be exacerbated in a tropical climate [24], the combination treatment may be a particularly welcome alternative in such countries as Brazil.

APPENDIX: LIST OF INVESTIGATORS

Dra Carmem Amaro (co-inv.), Botucatu
 Dr Paulo Jardim (PI), Goiania
 Dr Weimar Souza (co-inv.), Goiania
 Dr Fernando Almeida (PI), Sorocaba
 Dr Ricardo Augusto Cadaval (co-inv.), Sorocaba
 Dr Emílio Francischetti (PI), Rio de Janeiro
 Dra Márcia Tancredi (co-inv.), Rio de Janeiro
 Dr Luiz Carlos Bodanese (PI), Porto Alegre
 Dra Fernanda Dota (co-inv.), Porto Alegre
 Dr Artur Beltrame (PI), São Paulo
 Dr Eduardo Cantone Rosa (co-inv.), São Paulo

Dr Marco Antônio Mota Gomes (PI), Maceió
 Dra Maria Clara B. Brandão (co-inv.), Maceió
 Dra Andrea Brandão (PI), Rio de Janeiro
 Dra Maria Eliane Magalhães (co-inv.), Rio de Janeiro
 Dra Rosângela Milagres (PI), Minas Gerais
 Dr Paulo Henrique Waib (PI), Marília
 Dra Maria Isabel Gonçalves (co-inv.), Marília
 Dr Décio Mion (PI), São Paulo
 Dra Kátia Ortega (co-inv.), São Paulo
 Dr João Carlos Rocha (PI), Campinas
 Dr Augusto Terranova Rocha (co-inv.), Campinas
 Dra Maria Angélica B. Teixeira (co-inv.), São José do Rio Preto
 Dr Mauro Esteves Hernandez (co-inv.), São José do Rio Preto
 Dra Lilian Soares da Costa (PI), Rio de Janeiro
 Dra Mônica Amorim (co-inv.), Rio de Janeiro
 Dr Francisco Kerr Saraiva (PI), Campinas
 Dra Maria Helena Vidotti (co-inv.), Campinas
 Dr Roberto Sá Cunha (PI), Vitória
 Dr Francisco Fonseca (PI), São Paulo
 Dra Maria Cristine O. Izar (co-inv.), São Paulo
 Dr Hilton Chaves (PI), Recife
 Dr José Roberto da Silva (co-inv.), Recife
 Dr Luiz Antônio Ribeiro Introcaso (PI), Brasília

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Address for correspondence:

Suely Goldflus MD
 Novartis Biociências SA
 Av. Professor Vicente Rao, 90
 CEP: 04706-900
 São Paulo
 Brazil
 Tel: +55-11-5532-4333
 Fax: +55-11-5532-4228
 E-mail: suely.goldflus@pharma.novartis.com