CLINICAL SCIENCE

An economic evaluation of antihypertensive therapies based on clinical trials

Rosana Lima Garcia Tsuji,[I] Giovanio Vieira da Silva,[I] Katia Coelho Ortega,[I] Otávio Berwanger,[II] Décio Mion Júnior[I]

[I]Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, Nephrology Division, Hypertension Unit, São Paulo/SP, Brazil. [II]Instituto de Ensino e Pesquisa do Hospital do Coração HCor (Research Institute HCor) de São Paulo/SP, Brazil.

OBJECTIVE: Hypertension is a major issue in public health, and the financial costs associated with hypertension continue to increase. Cost-effectiveness studies focusing on antihypertensive drug combinations, however, have been scarce. The cost-effectiveness ratios of the traditional treatment (hydrochlorothiazide and atenolol) and the current treatment (losartan and amlodipine) were evaluated in patients with grade 1 or 2 hypertension (HT1-2). For patients with grade 3 hypertension (HT3), a third drug was added to the treatment combinations: enalapril was added to the traditional treatment, and hydrochlorothiazide was added to the current treatment.

METHODS: Hypertension treatment costs were estimated on the basis of the purchase prices of the antihypertensive medications, and effectiveness was measured as the reduction in systolic blood pressure and diastolic blood pressure (in mm Hg) at the end of a 12-month study period.

RESULTS: When the purchase price of the brand-name medication was used to calculate the cost, the traditional treatment presented a lower cost-effectiveness ratio [US$/mm Hg] than the current treatment in the HT1-2 group. In the HT3 group, however, there was no difference in cost-effectiveness ratio between the traditional treatment and the current treatment. The cost-effectiveness ratio differences between the treatment regimens maintained the same pattern when the purchase price of the lower-cost medication was used.

CONCLUSIONS: We conclude that the traditional treatment is more cost-effective (US$/mm Hg) than the current treatment in the HT1-2 group. There was no difference in cost-effectiveness between the traditional treatment and the current treatment for the HT3 group.

KEYWORDS: Hypertension; Pharmacoeconomics; Cost-effectiveness; Antihypertensive drugs.

INTRODUCTION

Studies have demonstrated that hypertension is a major health problem that is associated with high morbidity and mortality rates, and the costs associated with hypertension continue to increase (1,2). In most western countries, the costs of hypertension treatment account for a substantial portion of health resources (3).

Hypertension is also a significant issue in Brazil, and diseases related to hypertension are responsible for high hospitalization rates (4). Nevertheless, Brazilian pharmacoeconomic studies related to hypertension have been rare (5). The few studies that have examined antihypertensive treatment costs in Brazil concluded that diuretics and beta-blockers are more cost-effective than other classes of antihypertensive drugs (6).

To date, no pharmacoeconomic studies have analyzed the cost-effectiveness (C/E) ratio of antihypertensive drug combinations, which are recommended by several international guidelines for hypertension treatment (4,7). Antihypertensive drug combinations were designed to provide better control of hypertension, reduce the occasional adverse effects, improve treatment compliance in patients, and potentially reduce costs (8).

The objective of the present study was to evaluate the C/E ratios of two antihypertensive therapeutic drug combinations (i.e., hydrochlorothiazide plus atenolol *versus* losartan plus amlodipine) in patients with different grades of hypertension.

MATERIAL AND METHODS

Study Design

The economic analysis in this study was based on the results of a randomized open clinical trial that compared

two antihypertensive drug combinations: a thiazide diuretic plus a beta-blocker and a calcium channel blocker plus an angiotensin II receptor antagonist. Randomization was performed by means of drawing from envelopes, and the patients were followed for a period of 12 months (9).

The patients in the present study were referred to the Hypertension Unit of the University of São Paulo General Hospital. The research protocol was approved by the Ethics Committee of the University of São Paulo General Hospital. After receiving an explanation of the study, all of the patients signed a free and informed consent form to participate in the study.

Inclusion and exclusion criteria

This study included male and female patients who were diagnosed with essential hypertension and were older than 18 years. Patients with a body mass index $>40 \text{ kg/m}^2$, diabetes mellitus, chronic kidney disease, congestive heart failure, coronary artery disease, and/or stroke were excluded.

After the selection, the patients were categorized into two groups on the basis of their blood pressure in accordance with the European Society of Hypertension classification (7):

- Grade 1 and 2 hypertension (HT1-2): systolic blood pressure (SBP) ≥140 mm Hg and <180 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg and <110 mm Hg.
- Grade 3 hypertension (HT3): SBP ≥180 mm Hg and/or DBP ≥110 mm Hg.

Study Protocol

The drug treatments evaluated by this pharmacoeconomic analysis were based on combinations of low doses of two or more classes of antihypertensive drugs. The traditional treatment (TT) was based on the combination of a thiazide diuretic (hydrochlorothiazide) with a beta-blocker (atenolol) for the HT1-2 group, and an angiotensin-converting enzyme inhibitor (enalapril) was added to the treatment cocktail for the HT3 group. The current treatment (CT) was based on the combination of an angiotensin II receptor antagonist (losartan) with a dihydropyridine-type calcium channel blocker (amlodipine) for the HT1-2 group, and a diuretic thiazide (hydrochlorothiazide) was added to the treatment cocktail for the HT3 group.

The patients were randomized to receive either the TT or the CT regimen. When blood pressure (BP) control was not achieved (SBP<140 mm Hg and/or DBP<90 mm Hg), treatment steps were changed according to the protocols shown below:

- Drug treatment regimens for the HT1-2 group:

Step 1 BP ≥ 140/90 TT atenolol 25 mg + HCTZ 6.25 mg – twice a day
CT amlodipine 2.5 mg + losartan 25 mg - twice a day
Step 2 BP ≥ 140/90 TT atenolol 50 mg + HCTZ 12.5 mg - twice a day
CT amlodipine 5 mg + losartan 50 mg - twice a day
Step 3 BP ≥ 140/90 TT atenolol 50 mg + HCTZ 12.5 mg + enalapril 10 mg - twice a day
CT amlodipine 5 mg + losartan 50 mg + HCTZ 12.5 mg - twice a day

- Drug treatment regimens for the HT3 Group:

Step 1 BP ≥ 180/110 TT atenolol 50 mg + enalapril 10 mg + HCTZ 6.25 mg - twice a day
CT amlodipine 2.5 mg + losartan 25 mg + HCTZ 6.25 mg - twice a day
Step 2 BP ≥ 140/90 TT atenolol 100 mg + enalapril 20 mg + HCTZ 12.5 mg - twice a day
CT amlodipine 5 mg + losartan 50 mg + HCTZ 12.5 mg - twice a day
Step 3 BP ≥ 140/90 TT atenolol 100 mg + enalapril 20 mg + HCTZ 12.5 mg + clonidine 0.1 mg - twice a day
CT amlodipine 5 mg + losartan 50 mg + HCTZ 12.5 mg + clonidine 0.1 mg - twice a day

During the 12-month follow-up period, each patient was scheduled for seven medical visits with a 60-day interval between each appointment. Occasionally, unscheduled medical appointments had to be made for patients presenting a clinical intercurrence.

The total amount of medication necessary for 12 months of treatment was supplied to the patients at the end of each visit. Because 10% more pills were supplied, the remaining pills were counted at the next visit, and adherence was calculated on the basis of the number of remaining pills.

Any possible drug combinations that were not foreseen in the study protocol were named ''other combined treatments'' (OCTs). Thus, several combinations were possible at the end of the study as a result of reductions in drug doses and withdrawal or inclusion of other antihypertensive drugs because the initial drugs were ineffective or caused adverse side effects.

Pharmacoeconomic Study

Cost analysis. The management of adverse events (exchanging antihypertensive medication, increasing or reducing the dose, doses of drugs not specified in the original protocol), unscheduled medical visits [based on the medical procedures pricing table in Brazil (www.ramb.org.br/CBHPM_4_Edicao.pdf)], and the antihypertensive drugs that were administered [based on the brand-name price (www.consultaremedios.com.br – January/2007)] were taken into account for the cost analysis according to the following equation:

$$TCCT \text{ or } TCTT - HT1-2 \text{ or } HT3 = \sum_{i=2}^{7} Cv_i$$

where
TCCT: total cost of current treatment
TCTT: total cost of traditional treatment
HT1-2: grade 1 or 2 hypertension
HT3: grade 3 hypertension
Cv = cost of consumed medication + unscheduled medical visits during the study.
The currency used was U.S. dollars (US$).

Other costs, such as scheduled medical visits and laboratory exams, were the same in both regimens and were not included in the cost analysis.

To assess the robustness of the results, the brand with the lowest market value was used, and the C/E ratio analyses were repeated.

Price per unit of therapeutic regimen medications (reference price in US$/lowest price in US$):

- amlodipine 2.5 mg = 1.82/0.47
- amlodipine 5 mg = 3.66/0.93
- amlodipine 10 mg = 6.71/1.68
- atenolol 25 mg = 0.98/0.42
- atenolol 50 mg = 1.51/0.69
- atenolol 100 mg = 2.62/1.25
- clonidine 0.1 mg = 0.20/0.20
- enalapril 10 mg = 2.40/0.70
- enalapril 20 mg = 2.40/1.04
- furosemide 40 mg = 0.72/0.31
- hydralazine 50 mg = 0.39/0.39
- hydrochlorothiazide 6.25 mg = 0.06/0.05
- hydrochlorothiazide 12.5 mg = 0.14/0.09
- losartan 25 mg = 0.93/0.87
- losartan 50 mg = 1.87/1.53
- minoxidil 10 mg = 1.48/1.48

Effectiveness measurement. For the TT and CT groups, the effectiveness of the treatment was defined as the value (in mm Hg) to which the drug treatment was able to reduce the patients' SBP and DBP after each medical visit. Thus, the treatment's effectiveness was represented by the following equation:

$$Treatment\ Effectiveness =$$
$$Final\ BP - Baseline\ BP$$

Incremental Cost. The incremental cost was calculated as the ratio of the cost difference to the effectiveness difference between the CT and the TT, which represents the additional cost and the effectiveness gained when the CT is compared with the TT:

$$CT\ Cost - TT\ Cost/CT\ Effectiveness - TT\ Effectiveness$$

Statistical Analysis. The number of analyzed patients was derived from the original clinical trial, which had been calculated to meet the main objectives of that study (9). The data from all of the patients were analyzed with an intention-to-treat analysis. Continuous variables are descriptively expressed as the mean $\pm$ standard deviation or the median with the first and third quartiles. The categorical variables are expressed as absolute and/or relative frequencies. Graphically, cost-effectiveness is represented as a boxplot on the logarithmic scale, and the median for each dataset is
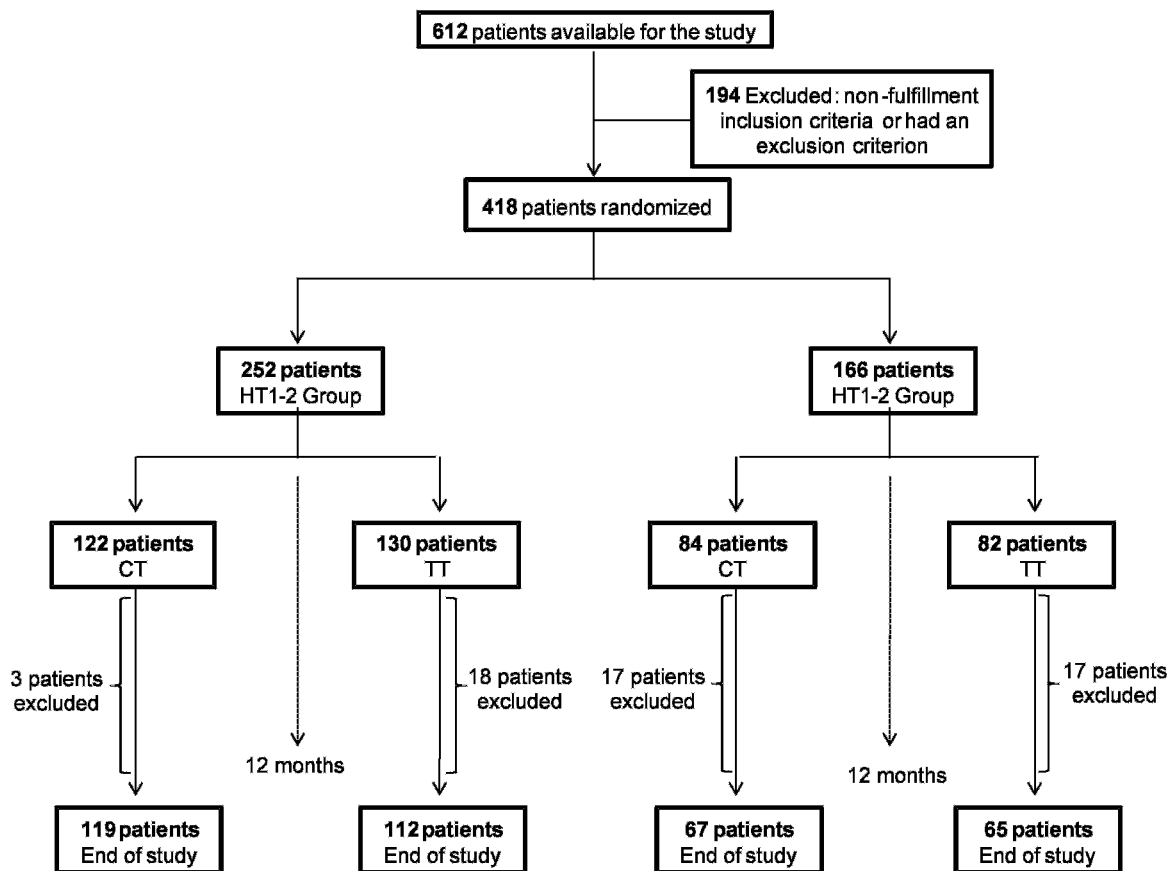
CT: Current Treatment; TT: Traditional Treatment

Figure 1 - Flowchart of the entry and discontinuation of patients for the pharmacoeconomic analysis.

Table 1 - Demographic and clinical characteristics.

	HT1-2		HT3	
	CT (n = 119)	TT (n = 112)	CT (n = 67)	TT (n = 65)
Gender (%)				
Male	25	24	46	37
Female	75	76	54	63
Ethnicity (%)				
Caucasian	58	64	13	9
Not Caucasian	42	36	43	49
Age (y)	52 ± 11	54 ± 11	52 ± 11	50 ± 11
SBP initial (mm Hg)	155 ± 12	154 ± 12	172 ± 23	172 ± 18
SBP final (mm Hg)	125 ± 14*	128 ± 15*	131 ± 18*	135 ± 22*
DBP initial (mm Hg)	92 ± 10	91 ± 9	112 ± 19	111 ± 17
DBP final (mm Hg)	73 ± 11*	72 ± 12*	78 ± 12*	80 ± 17*

SBP: systolic blood pressure; DBP: diastolic blood pressure.
*$p < 0.05$ between blood pressure values in the beginning and end of the study.
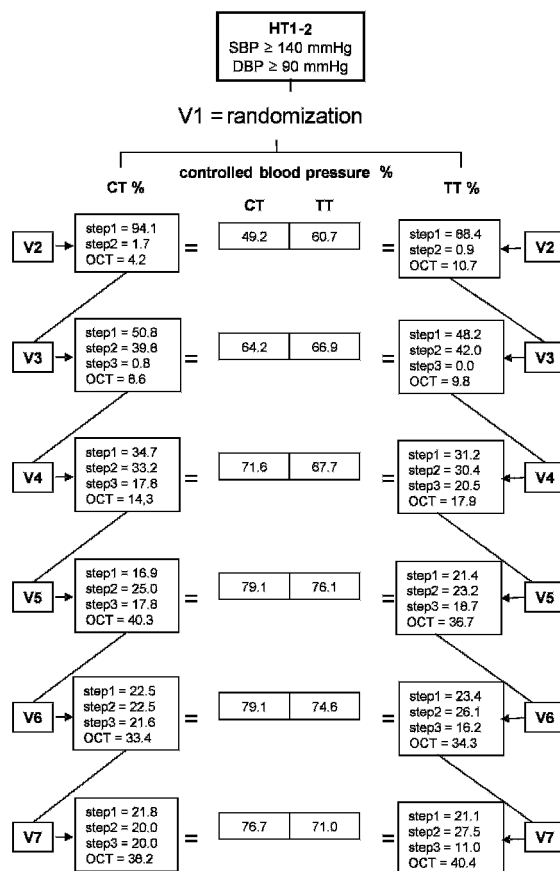
indicated by the black center line [the first and third quartiles are the edges of the box area, which is known as the interquartile range (IQR)]. The extreme values (within 1.5-fold of the interquartile range from the upper or lower quartile) are shown by the ends of the lines extending from the IQR. Points that lie more than 1.5-fold from the IQR are plotted individually (o). Values more than 3-fold the IQR (*). Distributions of continuous variables and categorical variables were compared by the Wilcoxon rank sum test and the chi-square test, respectively. Values of $p < 0.05$ were considered statistically significant.

RESULTS

After the recruitment, randomization, and follow-up period, we analyzed the results from 252 patients in the HT1-2 group: 130 patients in the TT group and 122 patients in the CT group. In the HT3 group, there were 82 patients in the TT group and 84 patients in the CT group (Figure 1). During the clinical study, three patients in the HT1-2 CT group and 18 patients in the HT1-2 TT group dropped out ($p < 0.05$). In the HT3 group, 17 patients in the two treatment arms were excluded (Figure 1).

Some demographic and clinical characteristics of the patients are shown in Table 1 (e.g., systolic and diastolic blood pressure values at the beginning and end of the study). Figures 2 and 3 show the proportion of patients upon each medical visit according to the corresponding step of the treatment and the percentage of patients who reached

Figure 2 - The percentage of patients with grade 1 or 2 hypertension (HT1-2) at each scheduled medical visit that reached the therapeutic target blood pressure and remained in the original protocol until the end of the study. The patients are divided according to their treatment group.
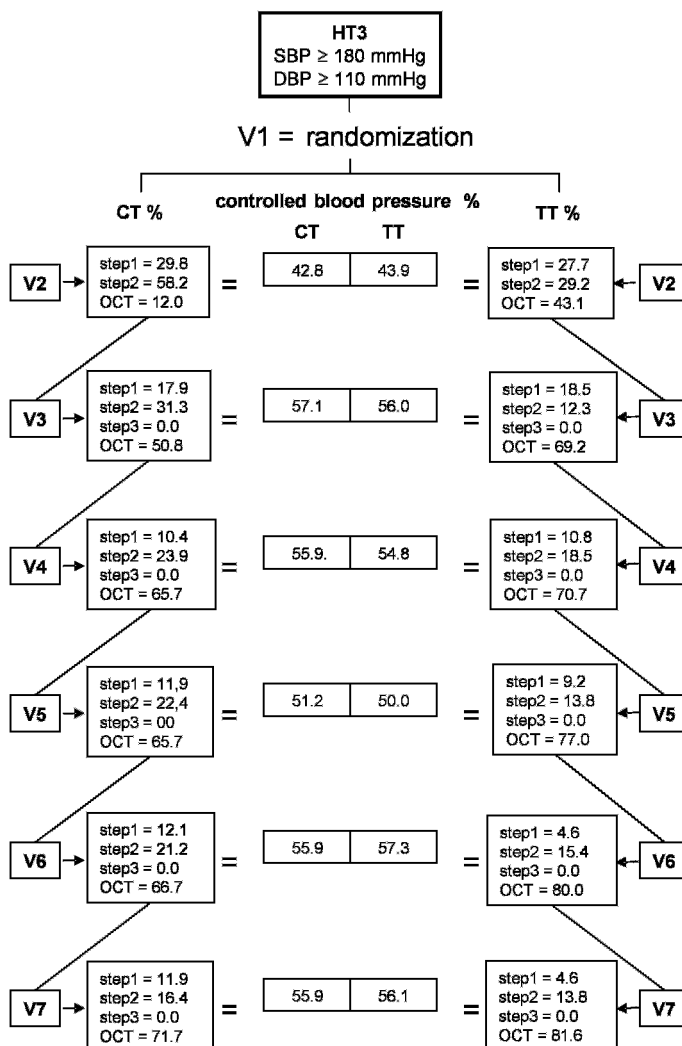
V= medical visit; OCT = other combined treatments; CT = current treatment;

TT = traditional treatment; SBP = systolic blood pressure; DBP = diastolic blood pressure

Figure 3 - The percentage of patients with grade 3 hypertension (HT3) at each scheduled medical visit that reached the therapeutic target blood pressure and remained in the original protocol until the end of the study. The patients are divided according to their treatment group.

the therapeutic target blood pressure in the HT1-2 and HT3 groups, respectively.

Importantly, there was no difference in the percentage of patients with controlled BP between the two treatment regimens (TT and CT) at the end of the study in either the HT1-2 group (71% and 76.7%, respectively) or the HT3 group (56.1% and 55.9%, respectively). In the HT1-2 group, however, the therapeutic target was reached in a higher proportion of patients compared with the HT3 group. When we analyzed the number of patients who used OCTs and remained in the protocol until the end of the study, we found that there was no difference regarding the TT and CT

Table 2 - Cost-effectiveness (C/E) ratios based on the purchase prices of the brand-names in patients with grade 1 or 2 (HT1-2) or grade 3 (HT3) hypertension. The data were analyzed according to the antihypertensive regimen used [i.e., the traditional treatment (TT) versus the current treatment (CT)].

C/E	HT1-2		p-value	HT3		p-value
	CT (n = 122)	TT (n = 130)		CT (n = 84)	TT (n = 82)	
US$/mm Hg SBP	83 (59 – 117)	41 (30 – 66)	0.0001	76 (56 – 124)	75 (55 – 141)	0.8446
US$/mm Hg DBP	120 (92 – 224)	61 (43 – 101)	0.0001	95 (74 – 129)	99 (69 – 171)	0.4570

Median (first - third quartiles); SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 3 - Incremental cost-effectiveness ratios.

	HT1-2		HT3	
	CT (n = 122)	TT (n = 130)	CT (n = 84)	TT (n = 82)
Total cost (US$)	314,648.76	158,206.42	286,666.47	276,660.03
Total reduction in SBP (mm Hg)	3,613.5	3,477.5	3,355	3,011
Incremental cost SBP (US$/mm Hg)	1,150.31		29.09	
Total reduction in DBP (mm Hg)	2,204.8	2,350.5	2,722.5	2,590
Incremental cost DBP (US$/mm Hg)	TT is dominant*		75.52	

*The TT was more effective and less costly than the CT.

regimens in the HT1-2 and HT3 groups, but a higher percentage of HT3 patients ended the study using OCTs.

Table 2 shows the C/E ratios [i.e., the cost (in US$) of reducing BP by 1 mm Hg at the end of the study]. For the HT1-2 group under the CT regimen, the C/E ratio (US$/mm Hg) was 83 (59–117) for SBP and 120 (92-224) for DBP when the purchase price of the brand-name medication was used to calculate the cost. These values were statistically lower for the TT regimen than for the CT regimen, with a C/E ratio of 41 (30–66) for SBP and 61 (43–101) for DBP ($p = 0.0001$). In the HT3 group, the C/E ratios were not statistically different between the TT and CT groups for either SBP or DBP.

Table 3 shows that in group HT1-2, the TT cost less and was more effective than the CT with regard to lowering DBP. The incremental cost per mm Hg for SBP in the HT1-2
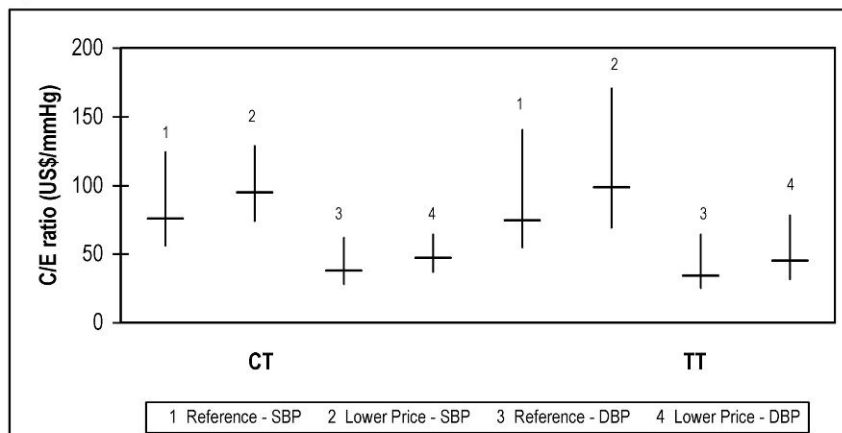

A) HT1-2
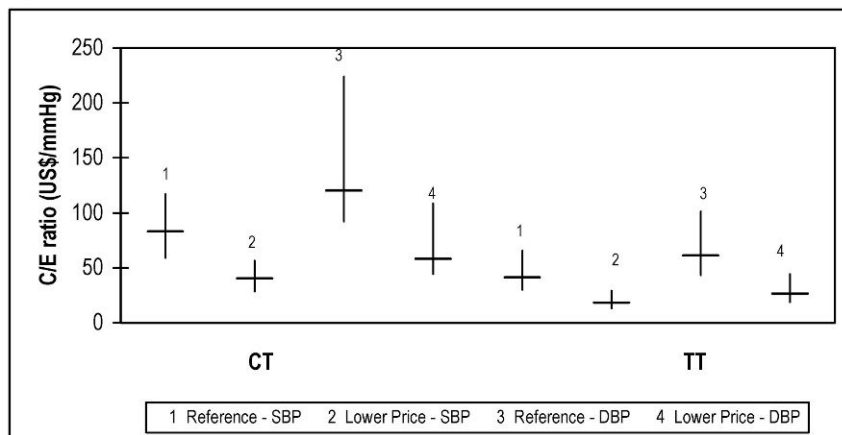
SBP: systolic blood pressure; DBP: diastolic blood pressure

p < 0.05 TT versus CT for all comparisons

B) HT3

SBP: systolic blood pressure; DBP: diastolic blood pressure

Figure 4 - Comparison of C/E ratios between the brand-name and lower-priced medications according to treatment regimen - current treatment (CT) versus traditional treatment (TT) - in patients with grade 1 or 2 hypertension (HT1-2 – Panel A) or grade 3 hypertension (HT3 – Panel B).

group was US$ 1,150.31. In the HT-3 group, however, the incremental cost per mm Hg for SBP and DBP was US$ 29.09 and US$ 75.52, respectively.

When we analyzed variations in the market prices of the medications (Figure 4), the TT continued to be more cost-effective than the CT when using the lower-price brand in HT1-2 patients. In the HT3 group, however, the C/E ratio did not display a statistically significant difference between the regimens.

Adverse events that occurred during the study were of mild or moderate intensity. Interestingly, more side effects were observed in the HT-3 group compared with the HT1-2 group. In the HT1-2 group, the patients who received the CT regimen showed more side effects than the patients who received the TT regimen, which was probably due to a higher prevalence of edema (Table 4). In the HT-3 group, however, there were no statistical differences regarding adverse events between the CT and the TT.

DISCUSSION

In all of the analyses that we performed, the antihypertensive treatment that used a thiazide combined with a beta-blocker was more cost-effective than the combination of a dihydropyridine-type calcium channel blocker and an angiotensin II receptor antagonist in HT1-2 patients. There was no difference, however, between the C/E ratios of these treatment regimens in grade 3 hypertensive patients.

In hypertension, the reduction of blood pressure in mm Hg is not the best measurement of the effectiveness of an antihypertensive treatment. Nevertheless, because of the difficulty of measuring long-term effects such as reductions in cardiovascular disease, reductions in blood pressure are still important data. Interestingly, several studies have shown that a DBP reduction of 4 mm Hg per year in a given population represents a 35 to 42% reduction in new potential cases of stroke (10,11).

In the present study, the C/E ratios favored the use of diuretics and beta-blockers, which corroborates the results of previous studies (12,13,14) The higher purchase costs of type 1 angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and calcium channel blockers

have already been considered by other authors (15,16). To the best of our knowledge, however, the present study was the first pharmacoeconomic analysis to examine C/E ratio differences between antihypertensive drug combinations.

Although an Italian study reported that diuretics and beta-blockers were cost-effective, the blood pressure of a large number of patients in that study remained uncontrolled after using these drugs (17). By contrast, in the present study the blood pressure of a large number of patients was controlled regardless of the drug combination that we used, especially in those with disease grades 1 and 2.

There was no statistically significant difference between the TT and CT regimens in the HT3 group, which contrasts with our results in the HT1-2 group. In the HT3 group, a large number of patients reached the end of the study using OCTs, which influenced the C/E ratio values even when considering that drug costs are lower for the TT than for the CT. Many of the patients in the HT3 group had their treatment changed to OCTs because they experienced a large number of side effects (Table 2), and the initial treatments may not have adequately controlled the blood pressure of the HT3 patients.

In Brazil, the use of epidemiological data from international studies to perform C/E studies is common. However, the present study included effectiveness and medication data that were obtained in Brazilian hypertensive patients. Although pharmacoeconomic analyses are complex, they provide an additional tool in the treatment decision-making process, and they should be included in the Brazilian health system guidelines to ensure a better distribution of health resources and to make the required medication available to hypertensive patients based on their specific status. Furthermore, the results of this pharmacoeconomic analysis may also be extended to other countries because the relative purchase prices of the analyzed classes of antihypertensive drugs are similar.

This study had some limitations. For example, it was an open study, and we did not perform a sensitivity analysis, which makes it difficult to extrapolate the results. Another limitation is the short follow-up period. Because antihypertensive treatment is a life-long regimen, 12 months may not be sufficient to reveal differences between the beneficial and adverse effects of the treatment regimens that we studied.

After considering the limitations of the present study, we conclude that the combination of a diuretic agent and a beta-blocker is more cost-effective for HT1-2 patients than treatment with a dihydropyridine-type calcium channel blocker and an angiotensin II receptor antagonist. Controlling blood pressure is harder in HT3 patients, and the present results did not identify a more cost-effective therapy; thus, the purchase cost of the medication should be secondary when achieving blood pressure control.

Table 4 - Number of patients showing side effects according to the antihypertensive regimen used – traditional treatment (TT) versus current treatment (CT) - in patients with grade 1 or 2 (HT1-2) or grade 3 (HT3) hypertension.

Side effect	HT1-2		HT3	
	TT (n = 130)	CT (n = 122)	TT (n = 82)	CT (n = 84)
Edema	6	28*	14	24
Cough	2	0	9	2*
Headache	7	3	11	9
Sexual Dysfunction	2	0	1	1
Dizziness	4	2	15	14
Cramps	1	2	1	1
Pain	4	3	4	9
Dry mouth	1	0	2	3
Miscellaneous	10	10	42	34
Total	37	48	99	97

*$p<0.05$ for the TT compared with the CT.

AUTHOR CONTRIBUTIONS

Tsuji RLG was responsible for the acquisition, analysis and interpretation of data, draft of the manuscript, and final approval of the version to be published. Silva GC was responsible for the analysis and interpretation of data, draft of the manuscript and final approval of the version to be published.

Ortega KC provided substantial contributions to the conception/design, and was also responsible for the acquisition, analysis and interpretation of data, critical revision of the manuscript for important intellectual content and final approval of the version to be published. Berwanger O was responsible for the analysis and interpretation of data, critical revision of the manuscript for important intellectual content and final approval of the version to be published. Mion Jr D provided substantial contributions to the conception/design and was also responsible for the analysis/interpretation of data, critical revision of the manuscript for important intellectual content and final approval of the version to be published.

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