Expedited blood pressure control with initial angiotensin II antagonist/diuretic therapy compared with stepped-care therapy in patients with ambulatory systolic hypertension

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OBJECTIVES: The present study investigated whether initiating therapy with a combination of losartan (L) and hydrochlorothiazide (HCTZ) allows for faster blood pressure (BP) control and fewer medications than the usual stepped-care approach in patients with stage 2 or 3 hypertension and ambulatory systolic hypertension.

METHODS: Patients with a mean daytime systolic ambulatory BP (ABP) of 135 mmHg or higher were randomly assigned to receive L 50 mg plus HCTZ 12.5 mg titrated to L 100 mg plus HCTZ 25 mg versus HCTZ 12.5 mg plus atenolol 50 mg. Amlodipine 5 mg was then added, if needed, to achieve a BP goal of less than 130 mmHg. Treatment titration was based on ABP.

RESULTS: Significantly more patients randomly assigned to L/HCTZ (63.5%) than stepped-care (37.5%; $P=0.008$) achieved the primary end point (daytime systolic BP of less than 130 mmHg). Initial L/HCTZ induced significantly greater decreases in ABP during each 24 h period after six weeks of therapy. Although reductions in systolic and diastolic ABP were not statistically different at the end of the study, ABP reduction was significantly greater ($P<0.001$) with the L/HCTZ-based regimen. Twice as many patients in the L/HCTZ group achieved the goal ABP with no more than two drugs (30.0% versus 14.7%; $P=0.03$). Moreover, tolerability was significantly better ($P=0.006$) in the L/HCTZ group, with a 40.0% incidence of adverse events, versus 65.6% in the stepped-care group.

CONCLUSION: Initiating antihypertensive therapy with the combination of L/HCTZ in patients with stage 2 or 3 hypertension and ambulatory systolic hypertension reaches a target BP faster in a higher proportion of patients, with fewer adverse events and less need for a third drug regimen than the conventional stepped-care approach.

Key Words: Antihypertensive therapy; Hydrochlorothiazide; Hypertension; Initial combination therapy; Losartan

Le contrôle accéléré de la tension artérielle avec une association d'antagoniste de l'angiotensine II et de diurétique par rapport à une thérapie par paliers chez des patients atteints d'hypertension systolique ambulatoire

OBJECTIFS : La présente étude a permis d'évaluer si l'instauration d'une thérapie associative de losartan (L) et d'hydrochlorothiazide (HCTZ) permet de contrôler la tension artérielle (TA) plus rapidement et de prendre moins de médicaments que les soins par paliers habituels chez des patients atteints d'hypertension de stade 2 ou 3 et d'hypertension systolique ambulatoire.

MÉTHODOLOGIE : Des patients dont la tension artérielle ambulatoire (TAA) systolique moyenne pendant le jour était d'au moins 135 mmHg ont été répartis au hasard pour recevoir 50 mg de L et 12,5 mg d'HCTZ titrés à 100 mg de L et 25 mg d'HCTZ par rapport à 12,5 mg d'HCTZ et 50 mg d'aténolol. On a ensuite ajouté 5 mg d'amlodipine, au besoin, pour obtenir la TA ciblée de moins de 130 mmHg. Le titrage du traitement dépendait de la TAA.

RÉSULTATS : Un nombre considérablement plus élevé de patients recevant au hasard la thérapie associative de L et HCTZ (63,5 %) plutôt que des soins par paliers (37,5 %; $p = 0,008$) a atteint le point de virage primaire (TA systolique pendant le jour inférieure à 130 mmHg). L'association initiale de L et HCTZ a suscité des diminutions significativement plus importantes de TAA pendant chaque période de 24 heures après une thérapie de six semaines. Bien qu'à la fin de l'étude, les réductions de TAA systolique et asystolique n'aient pas été différentes d'un point de vue statistique, la réduction de la TAA était beaucoup plus importante ($p < 0,001$) avec la posologie de L et HCTZ. Deux fois plus de patients de ce groupe ont atteint l'objectif de TAA sans prendre plus de deux médicaments (30,0 % par rapport à 14,7 %; $p = 0,03$). De plus, les patients présentaient une tolérabilité beaucoup plus élevée ($p = 0,006$) dans le groupe prenant le L et HCTZ, avec une incidence de 40,0 % d'effets indésirables par rapport à 65,6 % au sein du groupe recevant des soins par paliers.

CONCLUSION : L'instauration d'un traitement antihypertenseur associatif de L et HCTZ chez des patients atteints d'hypertension de stades 2 ou 3 et d'hypertension systolique ambulatoire atteignent une TA ciblée plus rapidement et en plus grande proportion, souffrent de moins d'effets indésirables et ont moins besoin d'un troisième régime posologique que ceux qui reçoivent des soins par paliers classiques.

Hypertension is a growing worldwide problem affecting more than 20% of the population. This pathology is associated with an increased risk of cardiovascular morbidity and mortality (1). In Canada, as in other countries, the burden of illness due to hypertension is excessively important in terms

of health care costs (1). Therefore, reducing blood pressure (BP) to target levels is mandatory, and it must be a priority to prevent clinical events in hypertensive patients. However, fewer than one-quarter of hypertensive patients are adequately controlled for hypertension (2,3). Furthermore, the control

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rate of systolic BP is particularly low (4,5); systolic BP prevails over its diastolic counterpart as a determinant of the overall cardiovascular risk profile (6,7). In keeping with this, one of the best strategies to improve BP control is to increase the use of treatment combinations in a fairly high proportion of hypertensive patients, especially in those with stage 2 and 3 essential hypertension (2). The prescription of adequate treatment combinations may thus improve the efficiency of treatment in increasing the number of patients reaching target BP. Indeed, a number of clinical trials have confirmed that successful treatment of hypertension requires combination therapy in the majority of patients (2-8). Consequently, there is a need to re-evaluate the current ways of treating hypertension, particularly the traditional stepped-care approach of initiating treatment with a single drug. One of the major obstacles to better BP control is clinical inertia. In fact, studies have found that the likelihood that a patient with uncontrolled BP has medications started or titrated upward is generally less than 20% (9). Therefore, a more aggressive approach to the initial management of hypertension, such as the use of combination therapy as first-line treatment, is more likely to achieve greater and faster BP control. Combination therapy with an angiotensin II antagonist and a thiazide diuretic provides additive efficacy through their different actions on the renin-angiotensin-aldosterone system (10). In a recent study (11), combinations of losartan 50 mg (L 50) and hydrochlorothiazide 12.5 mg (HCTZ 12.5), and L 100/HCTZ 25 provided a significant ambulatory BP (ABP) reduction, with a clear dose-response relationship (11).

The present study was designed to compare the efficacy of initial antihypertensive therapy using the fixed-dose combination of L/HCTZ with that of a stepped-care approach starting with HCTZ in patients with stage 2 or 3 systolic hypertension. Because casual BP has been shown to be a poor predictor of the daily BP profile and not as good as ABP in predicting target organ damage (12), the mean daytime systolic ABP was used to establish the clinical diagnosis of hypertension.

METHODS

The primary objective of the present study was to compare the percentage of patients achieving the target mean daytime systolic ABP of less than 130 mmHg (13) during 18 weeks of treatment, divided into three periods of six weeks each. In the first group, the treatment regimen consisted of a titration from the initial combination of L 50/HCTZ 12.5 to L 100/HCTZ 25, and finally to L 100/HCTZ 25 with amlodipine 5 mg. The other group was initially treated with HCTZ 12.5, to which atenolol 50 mg was added in the second period, and finally HCTZ 12.5 plus atenolol 50 mg and amlodipine 5 mg in the final period. Other objectives included comparing reductions in ambulatory and clinic systolic and diastolic BP, as well as pulse pressure, and comparing the percentage of patients of each treatment group reaching the goal systolic ABP with a two-drug regimen. This was a one-centre, prospective, randomized, open-label, blinded end point, parallel-group study (14). Outpatients older than 50 years of age with uncomplicated stage 2 or 3 systolic hypertension (clinic sitting systolic BP of 160 mmHg to 220 mmHg) were candidates for enrolment. Exclusion criteria were defined to enrol patients with minimal additional cardiovascular risk factors and included the following: patients with a history of ischemic heart disease, atrial fibrillation, cerebrovascular accident; and patients taking more than three antihypertensive medications at screening.

The protocol was approved by the local ethics committee. Written, informed consent was obtained before any procedure or withdrawal from antihypertensive medication was performed.

Study design

The study design is shown in Figure 1. After a washout period of two to four weeks, patients with a sitting systolic BP of 160 mmHg to 220 mmHg and a mean daytime (from 6:00 to 23:00) systolic ABP of 135 mmHg or higher (15) were randomly assigned to receive either L 50/HCTZ 12.5 or HCTZ 12.5 once daily. After six weeks, patients with a mean daytime systolic ABP of 130 mmHg or higher were prescribed L 100/HCTZ 25, or a combination of HCTZ 12.5 and atenolol 50 mg for a further six weeks. After 12 weeks of active treatment, patients with systolic ABP of 130 mmHg or higher were given L 100/HCTZ 25 plus amlodipine 5 mg, or a combination of HCTZ 12.5 plus atenolol 50 mg and amlodipine 5 mg for the last six weeks of the study.

Clinical evaluation

Patients attended the clinic between 7:00 and 9:00 and did not take their medication until various measurements were performed. The clinic BP was taken three times after patients had been seated for 10 min. Twenty-four hour ABP was measured at 20 min intervals between 06:00 and 23:00 (daytime), and at 30 min intervals between 23:00 and 6:00 (night-time) with a SpaceLabs monitor (model 90207, SpaceLabs Inc, USA). ABP monitoring (ABPM) was performed four times on a working weekday during the study, at the end of the washout period and at the end of each six-week treatment period. Accuracy of the ABP monitor was validated as previously described (16). The ABP readings had to meet satisfactory criteria, which were defined as a monitoring period of at least 24 h with at least one valid reading per hour and at least 75% of the programmed readings remaining after all data editing was completed. If the monitoring session did not satisfy these criteria, the recording was repeated within the next five days.

Compliance to study medication was evaluated by pill counting, and was arbitrarily considered adequate if the percentage of doses taken by a specific patient was between 80% and 120%, as defined in the vast majority of clinical study protocols.

Adverse events were investigated from spontaneously reported complaints and from direct nonleading questioning at the end of the washout period, as well as at each visit during the active treatment phase. Reported adverse events were then graded by the investigator as mild, moderate or severe in intensity according to accepted definitions (17).

Statistical analysis

Within-group comparison was based on one sample *t* test. ANOVA analysis was performed on changes from baseline for all clinical and laboratory values using an 'all patients treated last observation carried forward' approach. If the tested assumptions of normality and homogeneity of variance appeared to be violated, ANOVA analysis was performed on the log-transformed data or a nonparametric approach was applied. Fisher's exact test was performed on the percentage of patients who reached goal daytime systolic ABP and on the percentage of patients with adverse events. Differences were considered to be significant at $P < 0.05$.

RESULTS

Demographics

A total of 128 patients were considered for the study and were entered into the washout period. At the end of the washout

Figure 1 Design of study comparing the effects of fixed-dose combination therapy using losartan and hydrochlorothiazide (HCTZ) as initial therapy with the stepped-care approach using HCTZ as initial therapy. *Ambulatory blood pressure monitoring; †Titration or addition according to mean daytime ambulatory systolic blood pressure of 130 mmHg or higher

TABLE 1
Patient demographics

	Fixed-dose combination	Stepped-care approach	All patients
Study population, n	60	61	121
Sex, n (female/male)	21/39	19/42	40/81
Age, years (mean ± SD)	62.4±6.8	63.5±7.5	62.9±7.2
Duration of hypertension, years (mean ± SD)	14.9±12.5	14.8±11.3	14.9±11.7
Severity of hypertension, n			
Grade II	53	51	104
Grade III	7	10	17
Previously treated patients, n			
Yes	57	58	115
No	3	3	6

period, seven patients did not qualify for the active treatment period due to the criterion of not having the minimum required daytime systolic ABP. Therefore, 121 patients were randomly assigned in the study. Of these patients, 60 were allocated to the fixed-dose combination group (L/HCTZ-based treatment), and 61 patients were allocated to the stepped-care approach group (HCTZ-based treatment). All patients completed the study. Except for one patient of Asian origin randomly assigned to the stepped-care group, all patients were Caucasian, and 85% of patients were receiving combination therapy at baseline. As shown in Tables 1 and 2, both treatment groups were comparable with regard to demographic characteristics such as age, sex, clinic BP and mean daytime ABP. Medication compliance was demonstrated to be adequate, with 98% of patients having taken more than 95% of tablets.

Ambulatory and clinic BP

Mean (± SD) reductions in ABP and clinic BP from baseline during the different treatment periods are summarized in Table 3. There were significant mean changes in mean daytime, 24 h and night-time systolic ABP at weeks 6, 12 and 18 with both L/HCTZ- and HCTZ-based regimens (Table 3). The same pattern was observed for diastolic ABP, except at week 6, when BP decreases did not reach statistical significance during the 24 h interval period in the HCTZ monotherapy group.

TABLE 2
Clinic and ambulatory blood pressures before study treatment

	Fixed-dose combination	Stepped-care approach	All patients
Clinic blood pressure at screening, mmHg (mean ± SD)			
Systolic	143.0±12.3	141.8±13.6	142.4±12.8
Diastolic	88.1±7.4	87.7±8.4	87.9±7.8
Clinic blood pressure at baseline, mmHg (mean ± SD)			
Systolic	167.8±9.3	168.0±9.1	167.9±9.2
Diastolic	98.0±7.0	97.5±7.0	97.8±6.9
Daytime ambulatory blood pressure, mmHg (mean ± SD)			
Systolic	152.6±10.1	154.3±11.1	153.4±10.5
Diastolic	87.0±7.1	89.0±7.1	88.0±7.1

TABLE 3
Antihypertensive effects of study treatments on mean ambulatory and clinic blood pressure

	Fixed-dose combination group	Stepped-care approach group
Daytime ambulatory blood pressure, mmHg (mean ± SD)		
Baseline	152.6±10.1/87.0±7.1	154.3±11.1/89.1±7.1
Week 6	-9.8±8.2****/-4.4±5.0****	-2.2±7.6†/-0.06±5.4 (NS)
Week 12	-16.0±11.3/-8.0±6.4	-12.3±11.2/-8.1±7.0
Week 18	-22.3±11.6/-11.3±6.9	-20.1±9.9/-12.0±5.9
24 h ambulatory blood pressure, mmHg (mean ± SD)		
Baseline	148.0±9.5/83.7±8.9	149.4±11.2/85.4±8.5
Week 6	-9.5±8.1****/-4.3±4.8****	-2.6±7.6†/-0.21±5.3 (NS)
Week 12	-15.7±10.6*/-7.8±6.1	-11.8±10.6/-7.9±6.4
Week 18	-21.3±10.7/-10.5±6.5	-18.9±8.6/-11.3±5.1
Night-time ambulatory blood pressure, mmHg (mean ± SD)		
Baseline	136.9±11.2/75.7±9.3	137.4±13.9/76.6±8.9
Week 6	-8.8±10.9**/-4.0±6.5**	-3.4±10.2†/-0.87±6.25 (NS)
Week 12	-14.8±12.4/-7.6±7.7	-10.6±11.7/-7.5±6.1
Week 18	-19.0±11.9/-8.7±7.2	-16.1±9.3/-9.6±6.0
Clinic blood pressure, mmHg (mean ± SD)		
Baseline	167.8±9.3/98.0±7.0	168.0±9.1/97.5±7.0
Week 6	-17.7±13.4**/-6.7±8.6*	-10.3±12.9/-3.6±6.6
Week 12	-22.5±15.5/-8.5±8.3	-16.3±19.7/-7.3±7.7
Week 18	-28.3±15.0/-12.6±8.1	-24.4±12.8/-11.4±5.9

Values are presented as systolic blood pressure/diastolic blood pressure. Unless indicated, all differences were significant at $P<0.0001$ for both treatment versus baseline. * $P<0.05$; ** $P<0.01$; *** $P<0.001$; **** $P<0.0001$ for the fixed-dose combination group versus the stepped-care approach group. † $P<0.05$ versus baseline. NS Not significant

However, a difference in BP reduction between L/HCTZ and HCTZ treatments was found to be significant after six weeks of treatment during every 24 h interval period and at week 12 for the 24 h period. Additional decreases in ABP during each 24 h interval period with titration or add-on therapy were statistically significant ($P<0.001$), except when comparing night-time systolic BP between week 18 on L 100/HCTZ 25 plus amlodipine 5 mg and week 12 on L 100/HCTZ 25 (P not significant). Reductions in ambulatory pulse pressures from baseline following treatment with L/HCTZ or HCTZ were statistically significant at weeks 6, 12 and 18 during daytime (-5.4 mmHg, -8.0 mmHg and -11.0 mmHg versus -2.3 mmHg, -4.1 mmHg and -8.1 mmHg, respectively), 24 h

Figure 2) Histogram of the cumulative proportion of patients attaining the mean ambulatory daytime systolic blood pressure target of less than 130 mmHg at six, 12 and 18 weeks

(−5.2 mmHg, −7.8 mmHg and −10.8 mmHg versus −2.4 mmHg, −3.8 mmHg and −7.6 mmHg) and night-time (−4.8 mmHg, −7.2 mmHg and −10.3 mmHg versus −2.5 mmHg, −3.2 mmHg and −6.5 mmHg) periods. Of note, the differences between L/HCTZ and HCTZ groups were always statistically significant ($P < 0.001$), except at night after the first six weeks of therapy ($P = 0.06$).

Both treatment groups exhibited significant reductions in clinic systolic and diastolic BP at the different time points of the study compared with baseline ($P < 0.0001$). Systolic and diastolic BP reductions were significantly greater in the L/HCTZ group after six weeks of active therapy ($P < 0.01$ and $P < 0.05$, respectively). As observed in Table 3, there were discrepancies between clinic and ABP response to antihypertensive agents, especially after six weeks of treatment with HCTZ monotherapy (stepped-care). Indeed, the mean ($\pm$ SD) clinic BP reductions of -10.3 ± 12.9 / -3.6 ± 6.6 mmHg were significantly greater than that observed with ABPM (-2.2 ± 7.6 / -0.06 ± 5.4 mmHg; $P < 0.001$ for both systolic and diastolic BPs).

Attaining goal BP

The proportion of patients in each treatment group who achieved the mean daytime systolic ABP goal of less than 130 mmHg is shown in Figure 2. Significantly more patients achieved this goal in the fixed-dose combination group initially treated with L/HCTZ than in the stepped-care approach group on HCTZ monotherapy at all time points: after six weeks (18.3% versus 4.9%), 12 weeks (36.7% versus 19.7%) and 18 weeks (63.5% versus 37.5%).

BP control and number of antihypertensive drugs

The number and percentage of patients requiring two- or three-drug regimens by treatment group are presented in Table 4. In the group started on HCTZ alone, 85% of patients progressed to the final treatment group after 12 weeks of treatment. There were twice as many patients whose mean daytime systolic ABP was controlled with a two-drug regimen after

TABLE 4

Proportion of patients per treatment group on each of the possible regimens (n=121)

	Week 6, n (%)	Week 12, n (%)	Week 18, n (%)
Fixed-dose combination group (n=60)			
L 50/HCTZ 12.5	60 (100.0)	4 (6.7)	3 (5.0)
L 100/HCTZ 25	0	56 (93.3)	15 (25.0)
L 100/HCTZ 25 + amlodipine 5 mg	0	0	42 (70.0)
Stepped-care approach group (n=61)			
HCTZ 12.5	61 (100.0)	2 (3.3)	1 (1.6)
HCTZ 12.5 + atenolol 50 mg	0	59 (96.7)	8 (13.1)
HCTZ 12.5 + atenolol 50 mg + amlodipine 5 mg	0	0	52 (85.2)

HCTZ 12.5/25 Hydrochlorothiazide 12.5 mg/25 mg; L 50/100 Losartan 50 mg/100 mg

12 weeks of active treatment in the L/HCTZ group than in the HCTZ group (30% versus 14.7%, respectively; $P = 0.03$).

Adverse events

The proportions of patients with reported adverse events during the active treatment phase of the study were not statistically different between the L/HCTZ ($n = 40$; 66.7%) and the HCTZ ($n = 45$; 73.8%) groups. However, the proportion of clinical adverse events possibly, probably or definitely related to the study drugs was significantly higher ($P = 0.006$) in the HCTZ group ($n = 40$; 65%) than in the L/HCTZ group ($n = 24$; 40%). These events were generally of mild to moderate intensity.

DISCUSSION

The study population with elevated ambulatory systolic hypertension evaluated in our study was representative of the larger, multinational hypertensive population, in whom the incidence of elevated systolic BP has been reported to be more than 90% in patients over 50 years of age (18). The primary objective of the present study was to reduce the mean daytime systolic ABP to a target of less than 130 mmHg. Our findings demonstrated that the initial use of fixed-dose combination therapy with L/HCTZ resulted in a greater percentage of patients achieving target systolic BP compared with initial use of HCTZ monotherapy. Moreover, the significantly greater reductions in ambulatory pulse pressure during the 24 h interval at the end of each active treatment period are of considerable prognostic value. Indeed, a significant association has been noted between ABP and subsequent rate of cardiovascular morbid events, and such an association was independent of clinic systolic and diastolic BP (19,20). In light of our results, the greater decrease in pulse pressure suggests that this beneficial effect may be attributed to the greater antihypertensive efficacy provided by the fixed-dose combination treatment, rather than to the type of agents used. In addition, our data showed that the number of antihypertensive agents needed to achieve BP control was reduced in a fair number of patients who started on combination therapy. Furthermore, the initial combination therapy regimen was associated with better tolerability compared with a stepped-care therapeutic regimen. Therefore, our findings support the recommendations of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (2) and the European Society of Hypertension-

European Society of Cardiology (3), both of which recommend that drug combinations be used to initiate therapy in a large proportion of patients in whom single agents are unlikely to achieve BP targets.

By providing improved reduction of BP, the use of L/HCTZ, as in the present study, or other treatment combinations as initial therapies allows BP goals to be reached quickly in a greater proportion of patients. It is noteworthy that from the primary and secondary analyses of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial (8), early BP control was the strongest determinant of cardiovascular disease outcome, as demonstrated during the first three months of the study. However, these findings were not replicated in the recently published Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA) (21). In our study, the enhanced antihypertensive efficacy of L 100/HCTZ 25 compared with L 50/HCTZ 12.5 on ABP might have overcome the need for a complex and unpopular dose-titration procedure. From a clinical perspective, our results showing a higher proportion of hypertensive patients reaching target BP may be relevant. Indeed, the results demonstrate that synergistic treatment combinations may be used successfully in stage 2 and 3 hypertensive patients with systolic BP predominance. Consequently, better BP control and decrease in the number of medications needed that are associated with initial combination therapy, as observed in the present study, may improve compliance and provide more cost-effective treatment of hypertension. In fact, recent studies have shown that a considerable proportion of the total cost of antihypertensive treatment is due to factors such as inadequate BP control, poor compliance with therapy, discontinuation and switching between therapies (22). Moreover, a few studies based on hard morbidity and mortality end points, such as the ongoing Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial (23), have been undertaken, therefore identifying the need for such studies. We also observed better tolerability in the combination treatment group, which can be associated with differences in the type of antihypertensive agents used. Indeed, many studies have shown a higher rate of adverse events and, therefore, a lesser persistence to treatment in therapeutic strategy involving the use of beta-adrenergic blocking agents (24). In keeping with the previous assumptions, the 2006 Canadian Hypertension Education Program guidelines (25) were recently updated and now recommend the use of fixed-dose combinations to improve patient adherence to antihypertensive therapy.

By providing BP readings over a 24 h period, ABPM is a more precise tool for assessing the BP-lowering effects of antihypertensive drugs (26). From the present study, it is noteworthy that the decreases in clinic systolic and diastolic BP with HCTZ 12.5 mg were much greater than those observed during each interval of the 24 h readings with ABPM. Similar discrepancies between clinic and ABP response to antihypertensive agents have been reported previously (27-29) and suggest that ABPM is a more effective way of determining the response to antihypertensive therapies.

Limitations

The present study has some limitations. First, the design relies on the use of a combination therapy versus an antihypertensive agent used in monotherapy as first-line treatment. This

strategy may imply an imbalance in the study treatment. However, this is part of the originality of the present study, which aimed at mimicking real clinical practice. Indeed, because study treatments were adjusted on the basis of systolic ABP, it permitted us to intensify antihypertensive treatment only in patients not at target BP (ie, those who really needed it). Thus, we believe that both treatment groups were quite comparable, because treatments were intensified based on the same validated criteria, and because patients were treated with efficacious and synergistic combinations. However, it is mandatory to be cautious when interpreting these results, because the two treatment strategies used were pharmacologically different, although they have been demonstrated to be of similar antihypertensive efficacy. Second, because the present study was performed in one centre, the study population had to be carefully selected. In keeping with the characteristics previously shown, however, we think that our population was, indeed, highly representative of stage 2 hypertensive patients with systolic predominance. Finally, although the results of the present study clearly indicate improved BP control with initial therapy using a fixed-dose combination, they have to be substantiated by larger outcome studies.

CONCLUSION

In patients with stage 2 and 3 systolic hypertension confirmed by ABPM, an initial regimen with an angiotensin II antagonist/diuretic fixed-dose combination provided significantly greater control of BP. Moreover, ABP normalization was achieved in a shorter period of time with fewer medications and without increasing the overall rate of adverse events. The present study supports recent recommendations (2,3) for the initial use of combination therapy in high-risk patients. The results with dual therapy, using an angiotensin II antagonist combined with a diuretic, also suggest that this strategy should be further explored to determine whether better long-term control of hypertension can be obtained. Furthermore, large-scale clinical trials with morbidity and mortality end points need to be planned to further document the superior benefits of combination therapies versus monotherapies for the initial treatment of hypertension.

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