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Assessment of Antihypertensive Effect by Blood Pressure Monitoring: Applications to Bisoprolol and Lisinopril in a Double-Blind Study

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Summary: The aim of this study was to evaluate the antihypertensive effect of drugs according to the initial ambulatory blood pressure (BP) level. After a 15-day placebo run-in period, 105 patients with moderate essential hypertension (mean age, 52 years) underwent 24-h BP monitoring (spacelabs: 1 measure/15 min). Patients were subdivided into two groups: the "High" group, with 24-h mean values of systolic BP (SBP) >137 or diastolic BP (DBP) >87 mm Hg, and the "Low" group, with SBP ≤ 137 and DBP ≤ 87 mm Hg. All patients received, in a random and double-blind design, either bisoprolol (10 mg q.d.) or lisinopril (20 mg q.d.) for 8 weeks. At the end of this active treatment period, office and ambulatory BP measurements were performed. Casual measurements revealed similar BP decreases in all subgroups receiving bisoprolol and lisinopril; BP monitoring showed that the antihypertensive effect depended on the baseline mean 24-h value; −15/−12 mm Hg for bisoprolol and −18/−13 mm Hg for lisinopril in the High group; −7/−6 mm Hg for bisoprolol and −6/−6 mm Hg for lisinopril in the Low group. This study shows that the antihypertensive effect depended on initial ambulatory BP values, with a lower BP decrease in the Low group. Assessment of the antihypertensive effect on ambulatory BP is useful in clinical trials. **Key Words:** Ambulatory blood pressure monitoring—Lisinopril—Bisoprolol—Antihypertensive effect.

Ambulatory blood pressure (ABP) monitoring is now very useful and is recommended to assess the effect of antihypertensive drugs. It gives accurate information on BP profile and provides more detailed information than does office BP on first-dose effects, dose–response relations, and the duration of action of antihypertensive treatment (1–5). Patients are generally selected for study on the basis of office BP measurement alone, but some patients are normotensive when whole-day BP monitoring is performed (6). Thus it seems insufficient to limit the assessment of efficacy of an antihypertensive agent to office BP alone (7,8). Patients with hypertension with similar casual BPs are more susceptible to target-organ damage (9–12) and fatal and unfatal events (13,14) when the ABP is high. Furthermore, there is some evidence that antihypertensive responses differ between patients according to the pharmacologic classes of drugs and the 24-h BP (15–18). However, the separation of patients in two groups with high or low ABP in these studies was tested on a posteriori analysis, and β-blocker agents were not investigated.

The aim of this study was to evaluate the antihypertensive effect of a β-blocker and an angiotensin-converting enzyme (ACE) inhibitor on the basis of the initial ABP level in patients with mild to moderate hypertension, after stratification in two groups of high and low ABP.

PATIENTS AND METHODS

Patients

All patients had essential mild to moderate uncomplicated hypertension. Secondary causes of hypertension were ruled out by standard clinical and laboratory tests. Exclusion criteria included congestive heart failure, unstable angina pectoris, bradycardia, second-degree or third-degree atrioventricular block, hepatic and renal impairment, stroke or myocardial infarction within the last 3 months, childbearing potential, history of drug hypersensitivity, insulin-dependent diabetes, systemic disease,

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and concomitant medication known to interfere with ACE inhibitors or β-blockers and to affect BP.

All patients gave their written informed consent, and the protocol was approved by the la Timone hospital's Ethics Committee, Marseille.

Study design

Patients with hypertension were defined as those with a supine diastolic blood pressure (DBP) of 95–114 mm Hg. After inclusion in the study, patients entered a 2-week, single-blind, placebo, run-in period (4 weeks if they were previously treated with a diuretic).

On the final day of the placebo period, patients with mean supine DBP between 95 and 114 mm Hg underwent 24-h ABP monitoring (ABPM) and were then arbitrary subdivided into two groups: those whose mean 24-h systolic and diastolic ABP were >137 or 87 mm Hg (High group) and those whose mean 24-h ABPs were ≤137 and 87 mm Hg (Low group), according to the reference values of Staessen's meta-analysis published in 1990 (19).

Patients in each group were randomized and entered an 8-week, double-blind phase during which they received either bisoprolol, 10 mg q.d., or lisinopril, 20 mg q.d., After 4 weeks of treatment, patients whose supine DBP was ≥115 mm Hg or with systolic blood pressure (SBP) ≥200 mm Hg were excluded from the study. At the end of this phase, office BP measurements and ABPM were performed under the same conditions as on the last day of placebo period. ABP recordings were analyzed according to following validation criteria: ABP duration > 23 h, number of validated readings >48, and no more than two consecutive hours without readings. The range of validity for readings was 30 < DBP < 200 mm Hg, 50 ≤ SBP ≤ 300 mm Hg, pulse pressure ≥20 mm Hg if systolic BP >140 mm Hg, and pulse pressure ≥10 if SBP ≤140 mm Hg, 40 ≤ heart rate ≤ 200 beats/min.

Clinical procedures

BP was measured at each visit in the morning (between 8 and 10 a.m.) before the drug intake by using a mercury sphygmomanometer. The first and fifth Korotkoff sounds indicated the SBP and DBP, respectively. The average of three measurements taken every 2 min was considered for analysis. Response to treatment was defined as a decrease of DBP >10% of baseline DBP, and normalization as a SBP <140 mm Hg and a DBP <90 mm Hg. ABPM was performed at the end of the placebo run-in period and at the end of the double-blind treatment period with automated portable monitors (Spacelabs 90207), which recorded BP and heart rate at 15-min intervals throughout the day. The reliability of this device was checked by the investigator by using a concomitant mercury sphygmomanometer measurement at the beginning of the first recording. On the day of ABPM, the patient took the drug in front of the physician, just before the application of the device.

Hematologic and biochemical tests and electrocardiography were performed at entry. Spontaneous adverse events were noted at each visit.

Statistical methods

Casual blood pressure, clinical characteristics, and mean ABP were analyzed by using Student's paired *t* test between baseline values and those noted at the end of treatment.

Comparisons between drugs were performed by using an analysis of variance for office BP measurements and an analysis of variance and covariance for mean ABP measurements. Categoric variables were also compared by using the ξ^2 test. Data are given as mean ± standard deviation. The null hypothesis was rejected when the p value was <0.05.

Correlations between changes in BP after the introduction of treatment and initial BP values were determined after applying the transformation suggested by Oldham (20) to avoid the "law of the initial value" described by Gill et al. (21).

To compare decreases in office BP and ABP according to the initial office BP level, a second a posteriori analysis was performed: patients were subdivided into a Low group and a High group according to their initial office BP values (DBP ≤ 104 mm Hg and DBP > 104 mm Hg, respectively).

RESULTS

Of the 109 patients entering the study, four were placebo responders and 105 were allocated to the High (64) or Low (41) groups: 50 were randomized to receive bisoprolol and 55 to receive lisinopril. Nine patients were excluded from the primary efficacy analysis for the following reasons: two patients, nonqualifying baseline BP; one patient, missing data; four patients, lost to follow-up; and two patients, discontinuation of treatment because of adverse events. The primary efficacy analysis was performed on all patients who completed active treatment without protocol violation: 60 patients in the High group (bisoprolol, 30; lisinopril, 30) and 36 in the Low group (bisoprolol 18; lisinopril, 18). Demographic and baseline clinical characteristics are listed in Table 1: groups and treatments did not differ for sex, age, and weight. Both office and ABPs were significantly higher in the High group than in the Low group. In each of these groups, office and ABPs were not significantly different between patients treated with bisoprolol and those treated with lisinopril.

Office BP

Both bisoprolol and lisinopril caused significant ($p < 0.001$) reductions in SBP and DBP. The differences between treatments or between the High and Low groups were not significant (Table 2). In patients treated with bisoprolol, the decrease in heart rate was significantly greater (12.3 ± 9.7 vs. 0.1 ± 7.3 beats/min; 9.1 ± 7.3 vs. 4.8 ± 8.4 beats/min; $p < 0.001$) than in patients treated with lisinopril in both the High and Low groups (Table 2). In the High group, the response and normalization rates achieved 24 h after dose were 74 and 27% for bisoprolol and 66 and 33% for lisinopril, respectively (NS). In the Low group, these proportions were 89 and 72% for bisoprolol and 67 and 39% for lisinopril, respectively (NS).

Stratification according to ABP level

Mean whole-day reductions (from baseline to end of treatment) in systolic and diastolic ABPs observed in the High group and in the Low group are shown in Table 3.

In the High group, a similar and significant ($p < 0.001$) reduction in ABP was noted with both drugs during whole-day, daytime, and nighttime.

TABLE 1. *Demographics and baseline data*

Characteristics	Bisoprolol H. (n = 30)	Lisinopril H. (n = 30)	Bisoprolol L. (n = 18)	Lisinopril L. (n = 18)
Sex (%)				
Male	45.2	64.5	42.1	71.4
Female	54.8	35.5	57.9	28.6
Age (years)	55.7 ± 8.6	53.4 ± 10.4	50.6 ± 12.5	50.0 ± 10.6
Weight (kg)	74.6 ± 16	73.9 ± 13.2	71.2 ± 14	75.5 ± 13.2
Supine office BP (mm Hg)				
Systolic	164.2 ± 11.3	167.7 ± 16.2	153.0 ± 12.1[a]	156.9 ± 10.8[a]
Diastolic	102.3 ± 5.5	103.3 ± 5.6	98.3 ± 2.3[a]	100.0 ± 3.4[a]
Heart rate (beats/min)	74.2 ± 7.5	73.8 ± 8.8	76.1 ± 8	78.3 ± 9.3
24 h ambulatory BP (mm Hg)				
Systolic	147.5 ± 10.2	149.8 ± 10.6	126.1 ± 6.5[b]	128.5 ± 5.7[b]
Diastolic	93.1 ± 8.0	93.7 ± 6.8	79.5 ± 5.7[b]	81.4 ± 3.9[b]
Heart rate (beats/min)	76 ± 7.9	77.3 ± 9.7	74.9 ± 6.4	72.6 ± 8.5

H, High ambulatory blood pressure; L, Low ambulatory blood pressure.
[a]$p < 0.05$; [b]$p < 0.001$; bisoprolol H vs. L; and lisinopril H vs. L.

In the Low group, both drugs reduced BP to a lesser extent than in the High group, with differences depending on the period considered. Ambulatory SBP and DBP were significantly reduced during the 24-h and daytime periods. During the nighttime period, only bisoprolol significantly reduced DBP, whereas SBP was changed by none of the drugs. Statistical analysis showed no significant interdrug difference in the reduction of ambulatory SBP and DBP in the Low group.

Comparison between High and Low groups' SBP and DBP revealed, in both bisoprolol- and lisinopril-treated patients, statistically significant intergroup differences in BP reduction during the 24-h and night periods (bisoprolol: SBP, $p < 0.05$, $p < 0.05$; DBP, $p < 0.05$, $p < 0.01$; lisinopril: SBP, $p < 0.001$, $p < 0.001$; DBP, $p < 0.01$, $p < 0.01$). By contrast, daytime SBP and DBP did not differ significantly in the High and Low groups, even though their decrease was less marked in the Low group with each of the two drugs.

The consecutive hourly SBP and DBP values measured before and after treatment are shown in Fig. 1 (High group) and Fig. 2 (Low group). There was a greater decrease in ABP in the High group than in the Low group.

In patients randomized to bisoprolol, the reduction in heart rate was significantly greater in the High group than in the Low group (24 h, $p < 0.02$; daytime, $p < 0.05$; nighttime, $p < 0.05$).

Stratification according to office BP level

With a partition value of office DBP set at 104 mm Hg (Low group, DBP ≤ 104 mm Hg; High group, DBP > 104 mm Hg), no significant difference was observed regarding the decrease in DBP between the Low and High groups, either in patients receiving lisinopril (decrease in office DBP, 12.2 ± 6.0 vs. 14.4 ± 8.9 mm Hg; decrease in 24-h ADBP, 8.9 ± 8.1 vs. 12.9 ± 6.4 mm Hg; NS) or in those receiving bisoprolol (decrease in office DBP, 14.1 ± 5.2 vs. 13.5 ± 13.8 mm Hg; decrease in 24-h ADBP, 9.3 ± 8.7 vs. 10.8 ± 8.3 mm Hg; NS).

Relation between initial BP values and changes in BP

For the whole group (n = 96; Table 4), the 24-h ABP decrease was –12.8 ± 12.9/–9.8 ± 8.2 mm Hg. This decrease in BP was significantly greater in the High group (n = 60; –16.7 ± 13/–12.2 ± 8 mm Hg) than in the Low group [n = 36; –6.4 ± 10/–5.9 ± 7 mm Hg ($p < 0.001$)].

TABLE 2. *Office blood pressure, mean changes from baseline to end of treatment*

	Bisoprolol H. (n = 30)	Lisinopril H. (n = 30)	Bisoprolol L. (n = 18)	Lisinopril L. (n = 18)
Office blood pressure (mm Hg)				
Systolic	–19.1 ± 17.1[a]	–23.7 ± 14.1[a]	–20.7 ± 12.1[a]	–20.7 ± 13.8[a]
Diastolic	–13.7 ± 8.3[a]	–12.6 ± 7.1[a]	–14.6 ± 5.4[a]	–13.7 ± 7[a]
Heart rate (beats/min)	–12.3 ± 9.7[a]	–0.1 ± 7.3	–9.1 ± 7.3[b]	–4.8 ± 8.4[c]
Responders[d] (%)	74	66	89	67
Normalization[e] (%)	27	33	72	39

H, high ambulatory blood pressure; L, low ambulatory blood pressure.
[a]$p < 0.001$; [b]$p < 0.01$; [c]$p < 0.05$ compared with baseline values.
[d]Responder: DBP decrease > 10% of baseline DBP; [e]normalization: SBP < 140 mm Hg and DBP < 90 mm Hg.

TABLE 3. *Ambulatory blood pressure measurements. Mean changes from baseline to end of treatment*

	Bisoprolol H.			Lisinopril H.			Bisoprolol L.			Lisinopril L.		
	SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)	SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)	SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)	SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)
24 h	14.9 ± 14.1^a	11.7 ± 7.8^a	12.6 ± 7.6^a	18.4 ± 12^a	12.7 ± 8.2^a	2.6 ± 5^b	6.6 ± 11.9^c	6.1 ± 8.8^b	6.9 ± 7.2^a	6.2 ± 7.9^b	5.8 ± 4.8^a	0.2 ± 4.9
Day	15.5 ± 15^a	11.6 ± 8.6^a	14.3 ± 9.5^a	18.3 ± 12.5^a	12.9 ± 8.5^a	1.9 ± 5.3	8.2 ± 13.2^d	7.8 ± 10.6^b	8.9 ± 8.8^a	8.6 ± 7.6^a	7.3 ± 5.3^a	-0.4 ± 5.8
Night	13.5 ± 13.9^a	11.3 ± 8.5^a	9.3 ± 7.1^a	18.9 ± 17.3^a	12.5 ± 12.3^a	3.1 ± 6^a	4.8 ± 12.1	4 ± 7.6^c	4.8 ± 6.2^b	1 ± 12.9	2.5 ± 6.7	0.3 ± 6.3

H, High ambulatory blood pressure; L, Low ambulatory blood pressure.
$^a p < 0.001$, $^b p < 0.01$; $^c p < 0.05$; $^d p < 0.02$ vs. baseline.

Decreases in office BP did not differ between groups and treatments.

In the whole group of patients (n = 96), there was no correlation between the baseline level of office DBP and the magnitude of its change (r = 0.17; NS). Of note, the correlation between the baseline ambulatory DBP and the decrease in ambulatory DBP was significant (r = 0.46; $p < 0.001$), even after Oldham's transformation (r = 0.89; $p < 0.01$).

In the whole group (n = 96), there was a good correlation between the decrease in office BP and the decrease in ABP. The correlation was significant for SBP (r = 0.33; $p < 0.01$) and for DBP (r = 0.28; $p < 0.01$) and remained significant within each group.

Differences in office and ABP

A large difference between office BP and ABP values was observed (Table 5), similar in bisoprolol- and lisinopril-treated patients. This difference decreased after treatment ($p < 0.001$).

After stratification according to ABP, this difference was significantly higher in the Low group than in the High group at baseline ($p < 0.001$) and became similar after treatment.

DISCUSSION

Our study provides evidence that the effects of two different antihypertensive drugs (bisoprolol and lisinopril) depend on initial BP levels. Patients with higher initial ABP display a greater decrease in ABP (but not in clinic BP) with either drug than do patients with lower initial ABP levels.

These findings are not only the result of "the law of initial values" described by Oldham (20) and more specifically for antihypertensive drugs by Gill et al. (21) for the following reasons:

In our study, clinical therapeutic efficacy was identical in the High and Low groups.

There was a poor correlation in the whole group of our patients, between baseline clinic DBP and the decrease in clinic DBP (r = 0.17).

Similar results were not found for treatment-induced changes in office BP when patients were subdivided in Low and High groups according to office BP values.

In contrast, the correlation between baseline ambulatory DBP and the subsequent decrease in ambulatory DBP was significant even after Oldham's transformation (r = 0.89). This relation should therefore be considered definitely real.

A large difference between office and ABP was displayed, similar for the two treatments. This difference was strongly higher in the Low ambulatory group than in the High group at baseline, suggesting that the "alert reaction" to the physician was greater in the group with "white-coat hypertension" (22) than in the group with sustained hypertension. This difference declined after treatment, especially in the Low ambulatory group: de-

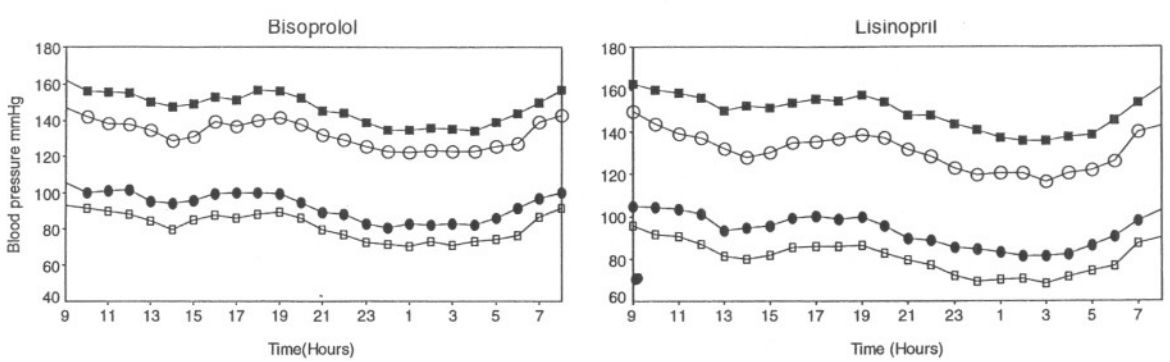

FIG. 1. Mean hourly systolic and diastolic blood pressure at baseline and during treatment in the High group.

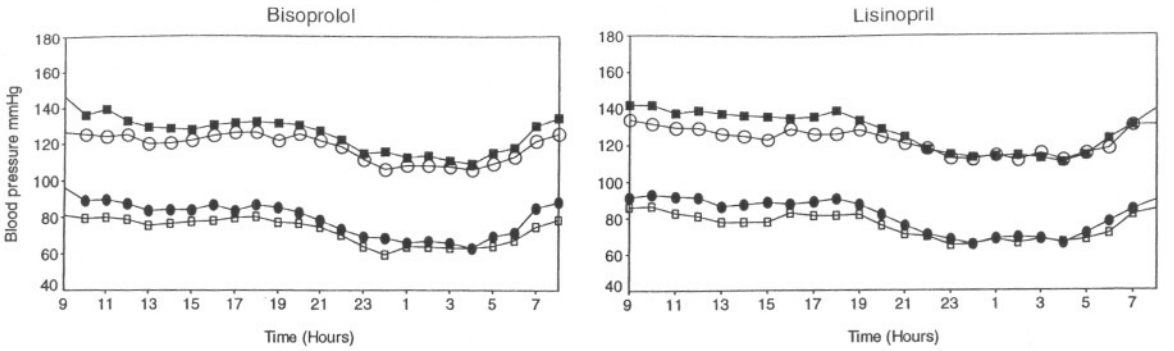

FIG. 2. Mean hourly systolic and diastolic blood pressure at baseline and during treatment in the Low group.

crease of the white-coat effect with treatment or with time? In the absence of a parallel placebo group, the effect of time could not be assessed in this study.

The originality of the design of our study is that subjects of both ABP groups were randomly allocated to one or the other treatment. Therefore the real impact of treatments could be exactly assessed in both High ABP patients (–16.7 ± 13/–12.2 ± 8 mm Hg) and low ABP patients (–6.4 ± 10/–5.9 ± 7 mm Hg). In contrast, the effect of treatment was diluted and could have been underestimated in the study population as a whole, in the absence of ambulatory stratification (–12.8 ± 12.9/–9.8 ± 8.2 mm Hg). This dilution effect has clinical implications, in particular regarding to the calculation of the "peak/trough" effect. Similar results were reported by Fagard et al. (24).

The smaller decrease in ABP in the Low group was observed both with the β-blocker (bisoprolol) and the ACE inhibitor (lisinopril), indicating the absence of a pharmacologic class effect, as previously reported in studies on calcium channel blockers (15–17). Two studies (17,23) reported that ACE inhibitors are more effective than calcium channel blockers in low-BP groups, and one recent trial showed that the effects of these two treatments were superimposable (18). However, the main aim of these studies was not to assess the effects of the two drugs according to initial ABP, and these studies therefore did not include randomization and β-blocker therapy.

TABLE 4. *Office and ambulatory blood pressure (n = 96)*

	D0	D56
Office BP (mm Hg)		
SBP	161.6 ± 14.3	140.6 ± 14.3[a]
DBP	101.4 ± 5.1	88 ± 8.1[a]
SBP decrease	—	21 ± 14.8[a]
DBP decrease	—	13.4 ± 7.2[a]
24-h Ambulatory BP (mm Hg)		
SBP	140.6 ± 13.7	127.8 ± 13.1[a]
DBP	88.5 ± 9.1	78.6 ± 8.9[a]
SBP decrease	—	12.8 ± 12.9[a]
DBP decrease	—	9.8 ± 8.2[a]

[a]$p < 0.001$ vs. baseline.

The lesser ambulatory efficacy of bisoprolol and lisinopril in the Low group was particularly marked at night (night DBP: bisoprolol, High 11.3 mm Hg/Low 4 mm Hg; lisinopril, High 12.5 mm Hg/Low 2.5 mm Hg). This cannot be explained by insufficient length of action, because the drugs were equally active at night and day in the High group, but rather seems to be the result of reduced activity of the two drugs when BP decreases nocturnally. Thus the risk of visceral hypoperfusion due to overmedication does not seem marked, as there appears to be an "efficacy threshold" below which antihypertensive treatment is less effective (17,24).

It is interesting to note that the bradycardic effect of bisoprolol was greater in the High group than in the Low group, despite an initially identical heart rate. This may be explained by the sympathetic nervous system intervention in the genesis of essential sustained hypertension.

Our findings have certain important practical implications:

The antihypertensive effect of a treatment (bisoprolol or lisinopril) depends on the initial ABP. Clinical measurement does not allow this distinction.

TABLE 5. *Difference between office and ambulatory blood pressure*

	D0	D56
Whole group (n = 96)		
DSBP (mm Hg)	20.8 ± 14.3	12.8 ± 12.3[a]
DDBP (mm Hg)	12.8 ± 8.2	9.4 ± 7.9[a]
Lisinopril (n = 48)		
DSBP (mm Hg)	21.7 ± 15.3	13.3 ± 13.7[b]
DDBP (mm Hg)	13 + 7.9	10.3 ± 8.3[c]
Bisoprolol (n = 48)		
DSBP (mm Hg)	20.1 ± 13	12.3 ± 10.9[b]
DDBP (mm Hg)	12.9 ± 8.6	8.4 ± 7.6[b]
Low Ambulatory Group (n = 36)		
DSBP (mm Hg)	27.3 ± 13.4	13.5 ± 10.9[b]
DDBP (mm Hg)	18.6 ± 5.6	10.7 ± 6.3[a]
High Ambulatory Group (n = 60)		
DSBP (mm Hg)	17.2 ± 13.5	12.4 ± 13[c]
DDBP (mm Hg)	9.6 ± 7.7	8.6 ± 8.7

DSBP, office–24-h ambulatory SBP; DDBP, office–24-h ambulatory DBP.

[a]$p < 0.001$, [b]$p < 0.01$, [c]$p < 0.05$.

The small reduction in ABP in the Low group, both with bisoprolol and lisinopril, limits the risks of overmedication.

This difference in efficacy with ABP should be used in the selection of patients in therapeutic trials: the real effect of a treatment could be diluted and underestimated if the initial ABP level is not taken into account.

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