Comparison of the Antihypertensive Efficiency of Nitrendipine, Metoprolol, Mepindolol and Enalapril Using Ambulatory 24-Hour Blood Pressure Monitoring

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In a randomized 6-month study of 201 patients, the antihypertensive efficiency of the calcium antagonist nitrendipine, the β_1-selective blocker metoprolol, mepindolol, the β blocker with intrinsic activity and the angiotensin-coverting enzyme inhibitor enalapril were compared as monitored by 24-hour ambulatory blood pressure (BP) measurements. The study was designed so that a comparable decrease in casual BP values was obtained with all 4 drugs. If normotension was not achieved with monotherapy, a diuretic also was administered. Pretreatment casual BP and mean 24-hour ambulatory BP values did not differ between the 4 groups. Normotension as assessed by casual BP measurements was observed in all 4 groups after 6 months of therapy, there being no significant differences between the groups. However, significantly more diuretics were required in the mepindolol (n = 14) and in the enalapril (n = 20) groups compared to the nitrendipine (n = 5) and metoprolol (n = 7) groups. Despite comparable casual BP control, the 4 groups differed significantly in their mean 24-hour measurements. The greatest systolic and diastolic BP decreases were seen in the metoprolol group. Metoprolol was also the most effective drug in decreasing the frequency of systolic pressure peaks >180 mm Hg. Both β blockers and enalapril significantly decreased the morning BP increase compared to the values before treatment, while nitrendipine did not. These data show that casual BP measurement is not a good predictor of 24-hour BP in patients taking hypertensive therapy. Despite an equal degree of "office" BP control, different antihypertensive regimens do not confer the same degree of "nonoffice" BP control.

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With improvement in technical equipment, noninvasive 24-hour ambulatory blood pressure (BP) determination is now increasingly used to monitor patients with systemic hypertension.[1,2] The underlying reason for such ambulatory monitoring is the large physiologic variability in BP. Casual cuff measurements do not allow one to predict BP behavior during the patients' normal activity.[3–5] Moreover, many patients respond to the doctor's appearance with a rapid increase in BP which can lead to unnecessary treatment with antihypertensive drugs.[6–8] Ambulatory BP monitoring may offer better control of BP in patients taking antihypertensive treatment.[9] However, it is not known whether drugs that show similar antihypertensive effects as assessed by casual BP measurements possess comparable antihypertensive efficacy during ambulatory monitoring. We have therefore performed a randomized study in which 24-hour ambulatory BP monitoring was evaluated in 201 patients with mild to moderate systemic hypertension before and after 6 months of treatment with the calcium antagonist nitrendipine, the β_1-selective blocker metoprolol, the β blocker with intrinsic activity mepindolol or the angiotensin-converting enzyme inhibitor enalapril. All of these drugs had normalized casual BP values as monotherapy or in combination with the diuretic hydrochlorothiazide.

METHODS

Patients were accepted into the study if they had a morning diastolic BP between 95 and 114 mm Hg during 3 casual measurements in the morning on 2 different days. In addition, >20% of BP values had to be >140/90 mm Hg during 24 hours of ambulatory BP monitoring. Patients were either untreated or antihypertensive therapy was discontinued for ≥4 weeks before BP measurements were obtained. Patients with secondary hypertension were excluded. Patients were randomly assigned to 1 of 4 groups treated with either nitrendipine 20 mg (Bayropharm, West Germany), metoprolol 100 mg (Astra, Sweden), mepindolol 5 mg (Schering, West Germany) or enalapril 10 mg (Merck Sharp & Dohme). The doses of the 4 substances were recommended by the companies for all 4 drugs for patients with mild to moderate hypertension and a single daily dose was administered at 8 A.M. Patients whose BP was not <140/90 mm Hg according to a casual BP

TABLE I Patient Characteristics, Casual Blood Pressure Before and Six Months After Therapy and Number of Prescribed Diuretics in the Four Groups

	Nitrendipine n = 50	Metoprolol n = 51	Mepindolol n = 49	Enalapril n = 51
Men	30	32	32	32
Women	20	19	17	19
Age (mean ± SD)	45 ± 15	43 ± 15	41 ± 14	44 ± 13
Casual blood pressure before therapy (mean ± SD)				
Systolic (mm Hg)	159 ± 13	163 ± 16	159 ± 15	163 ± 14
Diastolic (mm Hg)	100 ± 6	101 ± 6	100 ± 5	102 ± 6
Casual blood pressure after 6 months of therapy (mean ± SD)				
Systolic (mm Hg)	128 ± 9	130 ± 12	129 ± 11	133 ± 9
Diastolic (mm Hg)	83 ± 5	84 ± 7	82 ± 7	86 ± 7
No. of prescribed diuretics	5	7	14*	20*

* $p < 0.05$ compared with values in groups 1 and 2.
SD = standard deviation.

determination after 1 and 3 months were also given a diuretic (12.5 mg hydrochlorothiazide). Patients were excluded from the study if normotensive BP values were not achieved with this regimen. Twenty-four-hour BP measurements were repeated after 6 months of treatment in patients with normotensive BP according to casual BP control. Of 456 investigated patients, 299 could be included in the study. Of these 299 patients, 98 were excluded from the final evaluation—47 because of drug-related side effects and 51 because they did not fulfill the protocol. Of 201 patients who were normotensive at the end of the study, 50 were treated with nitrendipine, 51 with metoprolol, 49 with mepindolol and 51 with enalapril. Twenty-four-hour ambulatory BP registration was performed with the unit ICR 5200 (SpaceLabs). Measurements were performed every 15 minutes during the day (6 A.M. to 10 P.M.) and every 45 minutes during the night (10 P.M. to 6 A.M.). With this system,

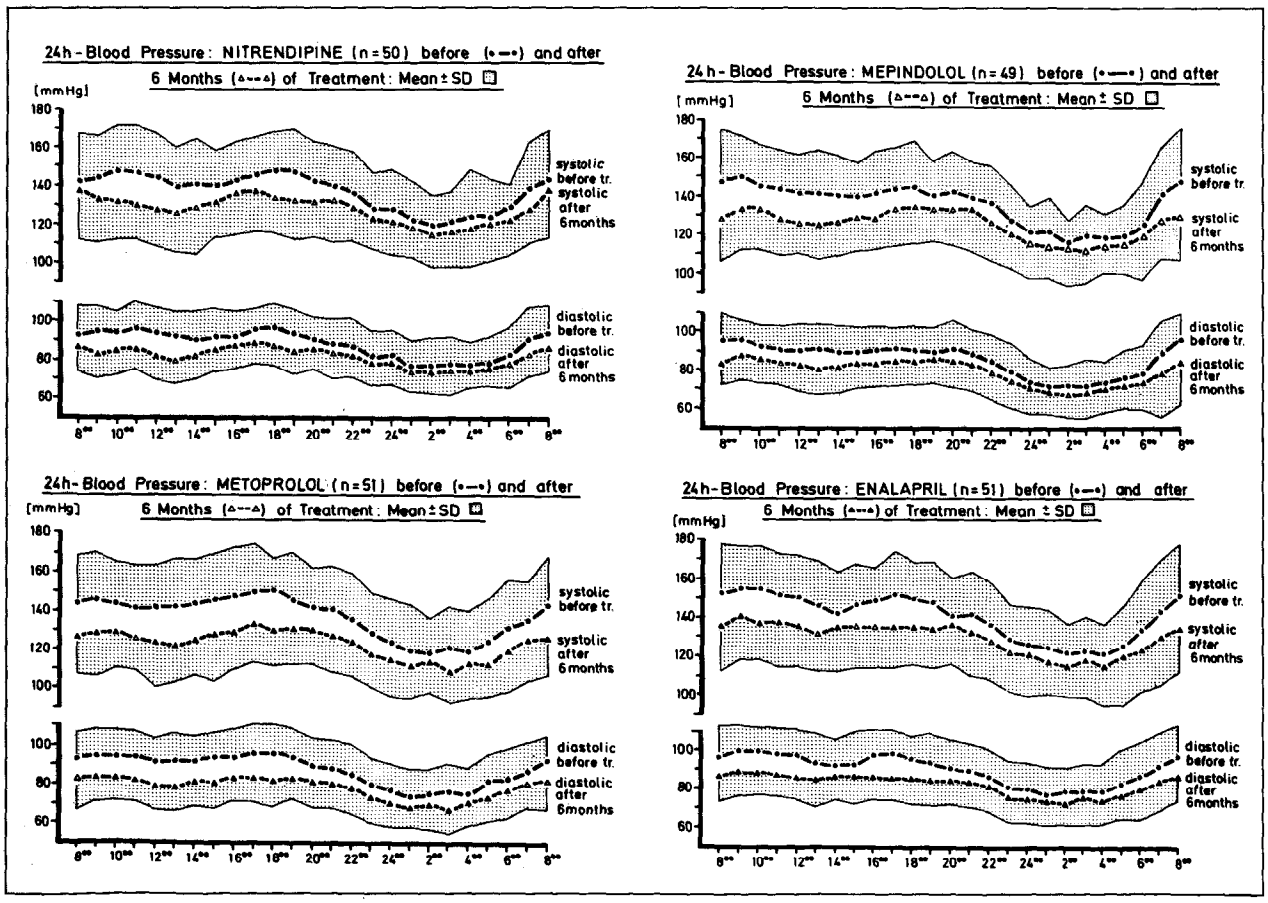

FIGURE 1. Twenty-four-hour blood pressure profiles of the 4 groups before and 6 months after therapy (hourly mean ± standard deviation). tr = treatment.

TABLE II Results of 24-Hour Blood Pressure Measurements

	All Patients		Difference After Six Months Compared with Initial Value				
			All Patients*	Nitrendipine	Metoprolol	Mepindolol	Enalapril
	0	6 Months					
	12,670	12,599	12,670/12,599	3,152/3,240	3,257/3,180	3,090/2,976	3,171/3,202
Mean BP during 24 hours							
Systolic (mm Hg)	139.8	127.8	−12.0	−10.4[2]	−15.0[1,7,8]	−11.1[6]	−11.7[6]
Diastolic (mm Hg)	89.5	81.3	−8.2	−7.6[2]	−10.2[1,3]	−6.9[2]	−8.3
Mean BP 6 A.M. to 10 P.M.							
Systolic (mm Hg)	143.3	130.1	−13.2	−11.6[2]	−16.1[1,7]	−12.0[6]	−13.1
Diastolic (mm Hg)	92.2	83.1	−9.1	−8.6[2]	−11.0[1,3]	−7.5[2]	−9.4
Mean BP 10 P.M. to 6 A.M.							
Systolic (mm Hg)	126.3	118.7	−7.6	−6.0[2]	−10.7[1,7,8]	−6.8[6]	−7.0[6]
Diastolic (mm Hg)	79.2	74.2	−5.0	−3.7[2]	−7.4[1,7,8]	−4.0[6]	−4.8[6]
No. values (%)							
Systolic							
>180 mm Hg	6.8	2.4	−4.4	−3.4[2]	−6.3[1,3,4]	−3.5[2]	−4.3[2]
>160 mm Hg	17.9	6.8	−11.1	−10.4[2]	−12.9[1,3]	−9.2[2,8]	−11.9[7]
>140 mm Hg	44.6	22.7	−21.9	−20.6[2,7]	−24.7[1,4,7]	−21.5[5,6]	−21.3[2]
Diastolic							
>100 mm Hg	22.3	6.2	−16.1	−15.8[2,3,4]	−18.5[1,3]	−10.4[1,2,4]	−19.7
>90 mm Hg	50.3	25.7	−24.6	−25.1[2,7]	−27.5[1,3,4]	−21.4[2,5]	−24.6[2]

* $p < 0.01$ compared with pretreatment values.
1–8: Significant differences between the groups after treatment.
1 = $p < 0.01$, 5 = $p < 0.05$ compared with the nitrendipine group.
2 = $p < 0.01$, 6 = $p < 0.05$ compared with the metoprolol group.
3 = $p < 0.01$, 7 = $p < 0.05$ compared with the mepindolol group.
4 = $p < 0.01$, 8 = $p < 0.05$ compared with the enalapril group.

BP is measured by auscultation with a microphone; if this method fails, BP is registrated by oscillometry. When ambulatory BP measurement was repeated after the treatment period, care was taken so that the patients' activities were comparable to those of the first measurement. With each patient, about 60 to 70 BP values per 24 hours could be analyzed.

Statistics: The frequency of elevated BP values was calculated from all BP values registered during a 24-hour period. Mean values and standard deviations per hour, per 24 hours and for the day and night were also computed. Casual morning BP controls are also given as mean values ± standard deviations. Statistical analyses of the frequency of elevated BP values before and after 6 months of treatment were performed with the chi-square test or Fisher's exact test for discrete variables. BP measurements were compared using nonparametric tests (Wilcoxon rank sum test, Kruskal-Wallis test). Student's *t* test for paired variables was used to test whether the mean difference in the norming BP increase before and after 6 months of therapy was significantly different from zero.

RESULTS

Patient characteristics are listed in Table I. The 4 groups did not differ in age, gender or entry BP values. The morning casual BP values are also listed in Table I. Normotension was observed in all 4 groups after 6 months of treatment; there were no significant differences among the groups. However, the number of patients requiring diuretics to achieve normotension was different—5 patients in the nitrendipine, 7 in the metoprolol, 14 in the mepindolol and 20 in the enalapril group. The first 2 groups differed significantly from the last 2 groups.

The 24-hour BP profiles of all 4 groups are shown in Figure 1. A circadian rhythm was always observed both before and after treatment. The posttreatment mean hourly BP values were lower than the pretreatment values when all 4 drugs were used. The results of the 24-hour ambulatory BP measurements are listed in Table II. Before therapy, 12,670 BP values could be evaluated and after therapy, 12,599 values. The 24-hour mean BP value from all patients decreased by 12 mm Hg systolic and 8.2 mm Hg diastolic after treatment. This decrease was more pronounced from 6 A.M. to 10 P.M. (13.2 systolic and 9.1 mm Hg diastolic) than from 10 P.M. to 6 A.M. (7.6 and 5.0 mmHg). Before treatment, 24-hour BP measurements did not differ significantly among the 4 groups. Despite comparable casual BP control, 24-hour BP measurements differed among the 4 groups. The greatest decreases in mean systolic and diastolic BPs were observed in the metoprolol group (15.0 and 10.2 mm Hg, respectively). Metoprolol reduced systolic BP more significantly during the 24-hour period than the other 3 groups and diastolic BP significantly more than nitrendipine and mepindolol. During the day, metoprolol caused a significantly greater decrease in mean ambulatory BP than either nitrendipine or mepindolol while, during the night, it was also more effective than enalapril. The frequencies of elevated BP values (percent elevated values during 24 hours) also varied. Metoprolol decreased the number of systolic pressure peaks >180 mm Hg more significantly than the other 3 drugs. The greatest decrease in the frequency of systolic values >160 mm Hg was also seen in the metoprolol group

followed by enalapril, nitrendipine and mepindolol. Metoprolol showed a significantly greater decrease of values >140 mm Hg after treatment compared to the other 3 groups. Diastolic values >100 mm Hg were decreased to the greatest extent in the enalapril group followed by metoprolol (both p values <0.01 in comparison to the 2 other groups), whereas mepindolol had the weakest effect. Diastolic values >90 mm Hg decreased to the greatest extent in the metoprolol group followed by nitrendipine and enalapril. Once again, the weakest effect was observed by mepindolol.

The rapid morning increase in BP (difference between the highest morning value before the drug was taken at 8 A.M. and the lowest night time value) also

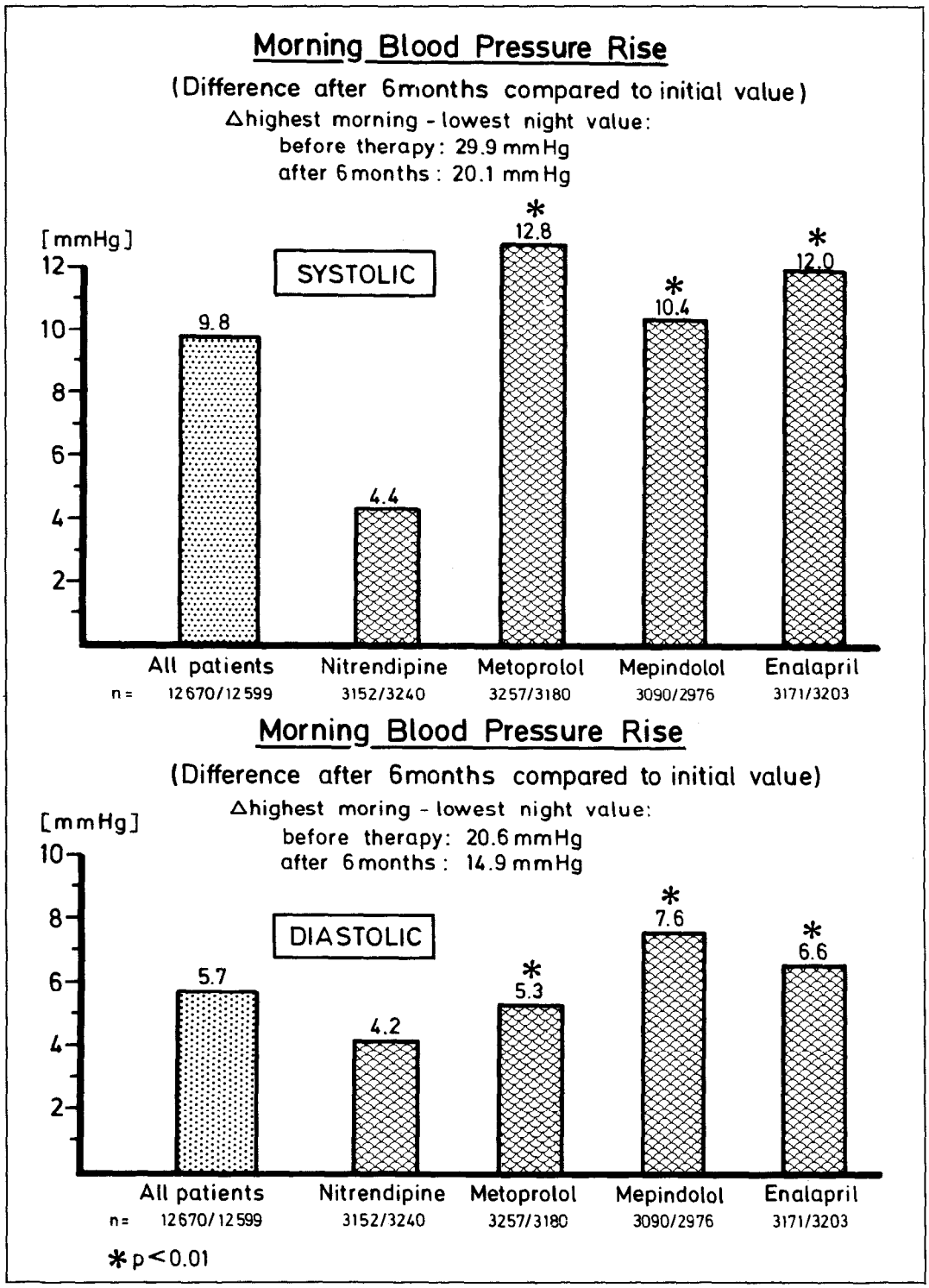

FIGURE 2. Morning blood pressure increase. *Significant differences in comparison to pretreatment values.

showed significant variation. Metoprolol, mepindolol and enalapril significantly decreased the systolic morning increase by 12.8, 10.4 and 12.0 mm Hg, respectively, and the diastolic increase by 5.3, 7.6 and 6.6 mm Hg compared to the values before treatment, whereas nitrendipine had no influence (Figure 2).

DISCUSSION

Twenty-four-hour ambulatory BP monitoring allows an improved assessment of BP and, as speculated by some investigators, of individual cardiovascular risk.[10-12] Perloff et al[13] showed that ambulatory BP values correlate more significantly to cardiovascular events than do casual BP measurements. Ambulatory BP best predicts cardiac end-organ damage and shows a stronger correlation to the incidence of cardiac hypertrophy.[12,14-16]

In this study, we compared the effects of 4 different antihypertensive drugs during 24-hour BP measurements after a 6-month treatment period in which all 4 drugs brought about a similar decrease in casual BP values into the normotensive range.

It could be shown that a similar decrease in casual BP values was not accompanied by a comparable effect during 24-hour BP monitoring. The β_1-selective blocking drug metoprolol exhibited the greatest systolic and diastolic decrease in mean 24-hour BP. This result was not related to an extended time of action, since a significant difference was also evident during the day (6 A.M. to 10 P.M.) when all groups showed antihypertensive effects. It is generally assumed that the cardiovascular damage in hypertension is related to the average level of BP and possibly also to the peaks associated with increased sympathetic activity. Metoprolol caused the greatest decrease in the frequency of elevated systolic values; in particular, systolic pressure peaks >180 mm Hg were 31 to 44% lower in this group compared to the other 3 groups. Whether intermittent BP peaks cause vascular damage in humans remains unproven.[6] However, there is some evidence from animal studies that such peaks can induce vascular damage accompanied by a segmental overstretching of the nonadapted vascular bed.[17,18]

A decrease in the number of hypertensive peaks must therefore be considered as clinically favorable. The number of elevated diastolic values >100 mm Hg decreased most obviously in the enalapril group followed by metoprolol; however, the greater number of diuretics necessary in the enalapril group should be noted. In combination with diurectics, enalapril proved to be an effective therapeutic regimen. Nitrendipine was less effective over 24 hours than metoprolol or enalapril, but required the lowest number of diuretics. The weakest effect on BP, especially on diastolic values, was observed in the mepindolol group despite the large number of diuretics administered.

BP exhibited a circadian rhythm increasing rapidly during the morning hours and then decreasing through a nadir around 3 A.M.[9,19,20] Current evidence suggests a possible link with cardiovascular events that have also been shown to occur most frequently during the morning hours. Stroke, transient ischemia and myocardial infarction all display a circadian rhythm similiar to that shown for arterial BP.[21-23] Although it is only speculation that the rapid increase in early morning BP is a mechanism in cardiovascular events, a role as contributing factor seems possible.[24] As a logical consequence, antihypertensive treatment should provide satisfactory BP control during the critical morning hours when arterial pressure is at its highest. In this study, metoprolol, mepindolol and enalapril significantly decreased the morning BP increase while nitrendipine did not. This might be due to a limited time of action for nitrendipine, and the lowest number of prescribed diuretics in the nitrendipine group must be noted. Other randomized studies dealing with different effects on the morning pressure increase with a sufficient number of treated patients are rare.[24] In all groups, the frequencies of elevated BP values (>140/90 mm Hg) after 6 months of treatment were greater than those of a collective group of normotensive patients investigated using the same methodology.[25] Thus, normotension achieved with antihypertensive therapy differs from "natural" normotension. This could be one explanation for the difference in mortality between treated hypertensive patients and normotensive patients.

The results of this study show that casual BP measurement is not a good predictor of 24-hour BP in patients receiving hypertensive therapy. Different antihypertensive regimens with an equal degree of "office" BP control do not confer the same degree of "nonoffice" BP control. In particular, the frequency of intermittent rapid increase in BP >180 mm Hg systolic and >100 mm Hg diastolic varied greatly among the groups, and there was a difference between the antihypertensive compounds in attenuating the early morning increase in BP. It is not known if an improved efficacy in antihypertensive treatment over 24 hours will improve cardiovascular prognosis in hypertensive patients. However, Wikstrand et al[26] observed a significant decrease in cardiovascular mortality with metoprolol compared to diuretics, despite a similar decrease in casual BP.[26] Although still speculative, an improved control of 24-hour BP may partly explain these differences.

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