Antihypertensive activity of angiotensin II AT_1 receptor antagonists: a systematic review of studies with 24 h ambulatory blood pressure monitoring

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Objective **To perform a systematic review of the antihypertensive activity of the angiotensin II AT_1 receptor antagonists (ARB).**

Methods **Studies in which blood pressure (BP) was measured using ambulatory BP monitoring for at least 24 h were collected from MEDLINE. Data for each treatment group, ARB, placebo or the drug used for its comparison were obtained from the selected studies. Only studies with a minimum of quality criteria were selected. The final study group contained 36 publications, with a total of 47 patient cohorts receiving ARB in monotherapy, 10 with placebo, 10 with amlodipine, and five with enalapril. The reduction in clinical and ambulatory BP during 24 h, day, night and the last 4-h period for each of the drugs analysed were calculated and adjusted by age, sex, number of participants and by the initial BP level.**

Results **The global antihypertensive activity of ARB differs from that observed with amlodipine in the sense that the magnitude of the reduction in the BP values does not essentially depend on the initial BP values nor on the dose used. When only ARB were considered, the drug used was a determinant for systolic BP reduction, whereas for diastolic BP the influence was on the BP reduction and the duration of the antihypertensive activity. The dose used had a particular influence on the duration of the antihypertensive activity for both systolic and diastolic BP.**

Conclusion **Among the ARB, the influence is on duration more than on the magnitude of BP reduction. Dose, therefore, is an important factor in the duration of antihypertensive activity. *J Hypertens* 25:1327–1336 © 2007 Lippincott Williams & Wilkins.**

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Introduction

Hypertension is a cardiovascular and renal risk factor with a high prevalence, and antihypertensive treatment can decrease hypertension-induced organ damage. Therefore, one therapeutic objective is to reduce arterial pressure values [1,2]. Within the available therapeutic arsenal, the last pharmacological group introduced has been the angiotensin II AT_1 receptor antagonists (ARB), and since its commercialization in 1994, seven active principals have been introduced: losartan, valsartan, irbesartan, candesartan, telmisartan, eprosartan and olmesartan [3,4]. ARB have a well-recognized antihypertensive activity, and although they share many common features, some pharmacokinetic and pharmacodynamic differences have been found among the components of the group [5]. A comparison of antihypertensive activity among the ARB, however, is a matter of debate because the published studies, even those with head-to-head comparison, have many confounding factors.

The introduction of ambulatory blood pressure monitoring (ABPM) has permitted a better assessment of antihypertensive activity, not only of the magnitude of the reduction, but also of its temporal profile [6,7]. In clinical studies analysing the antihypertensive activity of the ARB [8–75], the information offered in most cases is incomplete, varying widely from one study to another. The objective of the present study was to analyse the antihypertensive activity of ARB and the factors that determine this activity from a systematic review of the studies published in which blood pressure (BP) was assessed using 24-h ABPM.

Materials and methods

Published studies analysing the antihypertensive activity of ARB by using 24-h ABPM were selected. The search was performed on MEDLINE (www.ucbi.ulm.nih.gov) using articles published between 1 January 1994 and 30 April 2005, using 'ambulatory blood pressure monitoring', 'losartan', 'valsartan', 'candesartan',

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'irbesartan', 'telmisartan', 'olmesartan', and 'eprosartan' as key words.

Once the articles were reviewed, those matching the following criteria were selected for inclusion: (i) published in a peer-review journal; (ii) included patients treated with ARB as a study group; (iii) contained initial and final BP values or, when the latter were not explicit, the reduction of arterial pressure with the standard deviation; and (iv) obtained BP values over at least 24 h. The studies that did not have the necessary data for the analysis or that were published in more than one paper were excluded.

Data for each group of treatment, ARB, placebo or drug used to make comparisons, were obtained from the selected studies. When the therapeutic group was only represented in one or two of the selected studies, as in the case of hydrochlorothiazide or verapamil, only the ARB information was used. When hydrocholorotiazide was added on top of the ARB, the information was used to assess the additive effect of both drugs. For each treatment group, the following data were obtained: (i) the number of patients included; (ii) the demographic characteristics of age and sex; (iii) the drug and dose used; (iv) initial and final office systolic blood pressure (SBP) and diastolic blood pressure (DBP) values with their corresponding standard deviations; (v) both mean values of 24 h of initial and final SBP and DBP with their corresponding standard deviations, as well as values of the activity and sleep periods matching the criteria used to define these periods in each study; and (vi) the reduction of SBP and DBP values during the last 4–6 h of the interdose period. In cases in which BP values at the end of the treatment were not present, the mean values of the BP reductions with their corresponding standard deviations were obtained.

For each drug, three dose levels were considered if administered in monotherapy, and only one level was considered when administered with hydrochlorothiazide. The dose levels were low, titration or high. The low and high doses were: losartan 50–100 mg/day, valsartan 80–160 mg/day, irbesartan 150–300 mg/day, candesartan 8–16 mg/day, telmisartan 40–80 mg/day, eprosartan 600–900 mg/day, olmesartan 20–40 mg/day, amlodipine 5–10 mg/day; enalapril 20–40 mg/day; hydrochlorothiazide 25–50 mg/day. Titration doses were forced or dependent on the response.

Statistical methods

The initial values of SBP and DBP, both clinic and ambulatory, and the reduction in clinic and ambulatory BP values were calculated as adjusted means using the inverse variance for each drug, for ARB as a group, and for each ARB separately. The relationship between initial BP values and BP reduction was analysed using a meta-regression analysis, and the differences between the correlation coefficients were sought by using the method proposed by Chen and Popovich [76]. The influence of each drug and dosage on the magnitude of the office, 24-h, awake, sleep and the last 4–6 h BP reduction were analysed by analysis of variance test, covariate by the number of participants in each of the studies, the age and the initial BP values. The analysis was performed using the SPSS 11.1 statistical package for Windows (SPSS Inc., Chicago, Illinois, USA). Values of $P < 0.05$ were considered significant.

Results

General characteristics of the studies

Sixty-eight articles were found in the search conducted using previously defined criteria. Of these, 33 articles were excluded [8,10,13,15,17–21,28,33,37,40,41,46,47, 50–61,63,69,71,72,75]. Thirty were excluded because they were missing the necessary data, mostly the initial BP values. The other three were excluded because there was a partial or total data duplication in separate articles. The final study group was made up of 35 publications, with a total of 47 cohorts in ARB monotherapy, 10 with placebo, 11 with amlodipine, and eight with enalapril. The general characteristics of the studies included are shown in Table 1. For each of the groups, the final number of patients included in the analysis was 7040 with ARB in monotherapy, 601 with placebo, 1067 with amlodipine, and 606 with enalapril. The number of cohorts for both drug and dose, as well as for the number of patients, is shown in Table 2. There were no olmesartan and eprosartan forced titration studies. In addition, 17 cohorts with a total of 1757 patients in which hydrochlorothiazide was added to ARB were also included.

Most studies were performed in patients with essential arterial hypertension. Only in 1.4% of the cases was isolated systolic hypertension specified. Even though in most studies diabetes was among the exclusion criteria, some of the studies did not mention whether patients had diabetes or not.

Relationship between initial blood pressure values and antihypertensive activity

For comparative purposes among ARB and the comparators, correlation coefficients between initial SBP and DBP and the BP decrease were calculated, see Table 3. The relationship was significantly higher for clinic BP than for ambulatory BP. This was a consequence of true BP reduction, a decrease of the white-coat effect and a phenomenon of regression to the mean. It should be noted that the BP reduction with placebo implies a relationship with the initial BP levels for clinic BP that is less evident with ambulatory BP. Figure 1 shows the comparison between initial clinic and ambulatory SBP values and the BP reduction for amlodipine and the ARB group.

Table 1 Characteristics of the studies included in the analysis

	ARB		Placebo/comparative drug		
Author (ref.)	Drug (dose)	No. of subjects	Drug (dose)	No. of subjects	Study design
Neutel *et al.* [74]	Valsartan (20, 80, 160, 320)	44, 44, 41, 45	Placebo	42	DB
Fogari *et al.* [68]	Irbesartan (75, 150, 75 × 2)	55, 53, 57	Placebo	50	DB
Lacourciere *et al.* [27]	Candesartan (8–16) T	106	Placebo	32	DB
	Losartan (50–100) T	100			
Howe *et al.* [35]	Irbesartan (75–150) T	61	Placebo	51	DB
	Irbesartan/HCTZ (75 y 150/12.5) T	53			
Mallion *et al.* [73]	Losartan (50)	50	Placebo	53	DB
	Telmisartan (40–80) T	52, 52			
Littejohn *et al.* [66]	Telmisartan (80)	214			P
	Valsartan (80)	212			
White *et al.* [32]	Eprosartan (600, 1200)	59, 63	Placebo	55	DB
Zanchetti and Omboni [38]	Candesartan (4–8) T	72	Enalapril (10–20) T	67	DB
			Placebo	67	
White *et al.* [14]	Losartan (50–100) T	103/63	Enalapril (10–20) T	99	DB
			COER–Verapamil (240–360) T	109	
			Placebo	46	
Bakris [58]	Losartan (50–100) T	118	Enalapril (10–20) T	113	DB
			COER–Verapamil (240–360) T	116	
			Placebo	58	
Mancia *et al.* [23]	Ibesartan (150)	211			DB
	Valsartan (80)	215			
Coca *et al.* [34]	Irbesartan (150–300)	111	Enalapril (10–20) T	115	DB
Palatini *et al.* [25]	Valsartan/HCTZ (80/12.5)	133	Amlodipine (5–10) T	126	DB
Coca *et al.* [67]	Losartan/HCTZ (100/25)	41			O
Stergiou *et al.* [64]	Losartan (50)	33	Lisinopril (20)	33	C
Eguchi *et al.* [43]	Candesartan (4–8) T	35	Lisinopril (5–10) T	26	C
Lacourciere and Poirier [49]	Losartan/HCTZ (50–100 y 12.5–25) T	56	HCTZ (12.5–25)	55	DB
Brunner *et al.* [53]	Candesartan (8)	311			DB
	Olmesartan (20)	293			
Coca *et al.* [36]	Irbesartan/HCTZ (300/25)	57			O
Lacourciere *et al.* [65]	Losartan/HCTZ (50/12.5)	196			P
	Valsartan (40/12.5, 80/12.5)	195, 200			
Neutel *et al.* [11]	Valsartan (80)	197	Amlodipine (5)	206	M
	Losartan (50)	50	Placebo	129	
	Telmisartan (40)	124, 860			
Neutel and Smith [12]	Telmisartan (80)	338			P
	Losartan/HCTZ (50/12.5)	352			
Chrysant *et al.* [45]	Olmesartan (20)	171	Amlodipine (5)	172	DB
			Placebo	54	
Malacco *et al.* [39]	Valsartan/HCTZ (160/12.5)	45	Amlodipine (10)	40	P
White *et al.* [24]	Telmisartan (40–80) T	230			DB
	Valsartan (80–160) T	224			
Eguchi *et al.* [44]	Valsartan (40–160) T	38	Amlodipine (2.5–10) T	38	O
Palatini *et al.* [31]	Valsartan/HCTZ (80–160)	79	Amlodipine/HCTZ (5–10)	85	DB
Lacourciere *et al.* [22]	Telmisartan (40–80) T	468			DB
	Valsartan (80–160) T	462			
Poirier *et al.* [42]	Telmisartan (80)	18	Ramipril (2.5–5–10)	17	SB
			Amlodipine (5–10)	22	
Palatini *et al.* [62]	Valsartan (80–160) T	79	Amlodipine (5–10) T	85	DB
Radauceanu *et al.* [29]	Valsartan (40–80) T	117	Amlodipine (5–10) T	114	DB
Parra *et al.* [48]	Telmisartan (80)	89			O
De la Sierra *et al.* [9]	Losartan/HCTZ (50/12.5)	49	Enalapril/nitredipine (10–20)	45	DB
Smith *et al.* [26]	Irbesartan (150)	134			DB
	Losartan (50)	134			
	Olmesartan (20)	136			
	Valsartan (80)	130			
Fogari *et al.* [70]	Telmisartan/HCTZ (80/12.5)	62	Nifedipine GITS (60)	62	O

ARB, Angiotensin II AT_1 receptor antagonist; C, crossover; DB, double blind placebo controlled; HCTZ, hydrochlorothiazide; M, mix; O, open-label; P, open-label blinded end-point design; SB, single blind; T, titration.

Whichever BP was selected, SBP, DBP or the average of 24 h, day, night period and past 4 h, the correlation coefficients were better for amlodipine than they were for the ARB. Although the addition of the thiazidic diuretic improved the correlation coefficients, these did not reach the amlodipine values. This indicates that the proportionality between the initial value and the degree of reduction for amlodipine is not a feature of ARB. The behaviour of enalapril is intermediate between amlodipine and the ARB, but it remains closer to the former than to the latter.

Dosage influence

In the cohorts of amlodipine, enalapril and ARB, the influence of the dose was sought by analysis of variance in which the dependent variable was the reduction in BP

Table 2 Number of cohorts (patients) per therapeutic group and per drugs included

	Dose			
	Low	Titration	High	Total
Placebo	–	–	–	10 (601)
Amlodipine	3 (578)	4 (269)	4 (280)	11 (1067)
Enalapril	1 (99)	5 (381)	2 (126)	8 (606)
ARB	24 (3007)	13 (2256)	10 (1784)	47 (7047)
Losartan	5 (323)	2 (233)	1 (55)	8 (611)
Valsartan	7 (975)	5 (947)	2 (86)	14 (2008)
Irbesartan	5 (510)	1 (115)	0 (0)	6 (625)
Candesartan	1 (323)	3 (249)	0 (0)	4 (572)
Telmisartan	2 (181)	2 (712)	6 (1580)	10 (2473)
Eprosartan	1 (59)	0 (0)	1 (63)	2 (122)
Olmesartan	3 (636)	0 (0)	0 (0)	3 (636)
ARB plus HCTZ				17 (1757)

ARB, Angiotensin II AT_1 receptor antagonist; HCTZ, hydroclorothiazide.

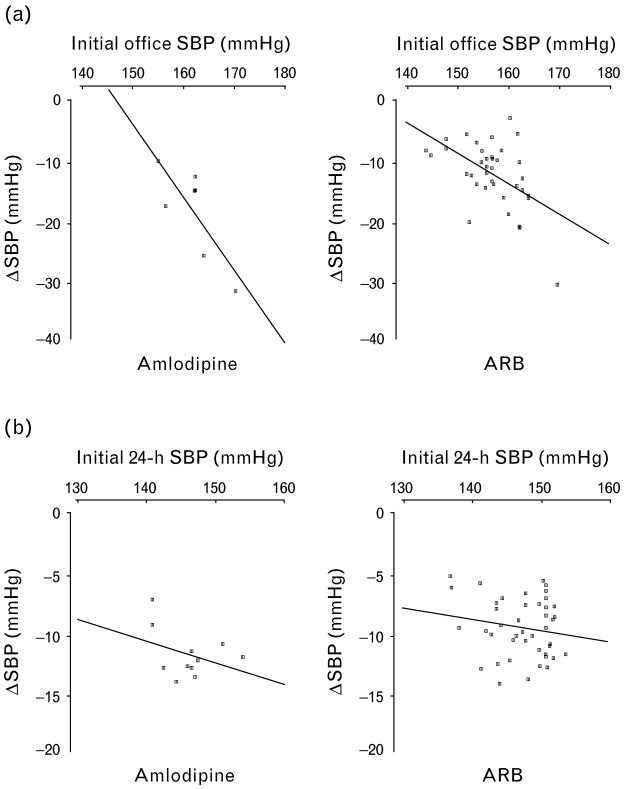
Table 3 Correlation coefficients between initial office and ambulatory systolic and diastolic blood pressure and the blood pressure reduction

	Placebo	Amlodipine	Enalapril	ARB	ARB + HCTZ
Office SBP	−0.25	−0.80*,†	−0.84*,†	−0.52*	−0.59*
Office DBP	−0.21	−0.82*,†	−0.69*,†	−0.44*	−0.68*
24-H SBP	−0.10	−0.36&	−0.48†	−0.17	−0.05
24-H DBP	−0.10	−0.21	−0.09	−0.20	−0.66*

ARB, Angiotensin II AT_1 receptor antagonist; DBP, diastolic blood pressure; HCTZ, hydroclorothiazide; SBP, systolic blood pressure. *Statistical significance ($P < 0.05$). † Statistical significance with ARB ($P < 0.05$).

values and the independent factors were the three different doses and the initial BP levels. The results were adjusted by the number of patients included in each study. In Table 4, the significance of the variance analysis is expressed for initial BP and dose analysed together. Clinic BP reduction, both SBP and DBP, was not influenced by the ARB dosage. Amlodipine and enalapril, however, reduced the ambulatory BP values of 24 h, day and night depending on the dose, the higher the dose the higher the BP reduction. In contrast, for the whole subset of ARB, the dosage did not influence the reduction in SBP or DBP values.

Fig. 1



Relationship between initial blood pressure (BP) and BP reduction in office (a) and ambulatory (b) systolic blood pressure (SBP) for amlodipine and angiotensin II AT_1 receptor antagonists (ARB). Correlation coefficients are office SBP −0.80 and −0.52 for amlodipine and ARB, respectively; average of 24-h SBP −0.36 and −0.17 for amlodipine and ARB, respectively.

Drug influence

Drug influence on the reduction in BP values, both clinic and ambulatory, was analysed for the ARB. For the SBP and DBP values, as well as for each ambulatory period, the antihypertensive activity of the specific drug was analysed, adjusted by the initial BP values, dose, age, and number of participants. The results are shown in Table 5

Table 4 Values of *P* for the influence of the initial blood pressure and dose on the reduction of office and ambulatory blood pressure values of 24-h, day and night periods, for each group studied

	Amlodipine		Enalapril		ARB	
	BP	Dose	BP	Dose	BP	Dose
Office SBP	0.27	0.09	0.36	0.58	0.06	0.40
Office DBP	0.94	0.22	0.42	0.66	0.48	0.99
24-H SBP	0.04	0.02	0.10	0.13	0.30	0.39
24-H DBP	0.02	0.07	0.03	0.04	0.33	0.56
Day SBP	0.04	0.02	0.07	0.03	0.14	0.56
Day DBP	0.01	0.03	0.04	0.07	0.56	0.82
Night SBP	0.02	0.09	0.15	0.09	0.34	0.12
Night DBP	0.05	0.24	0.04	0.18	0.18	0.04

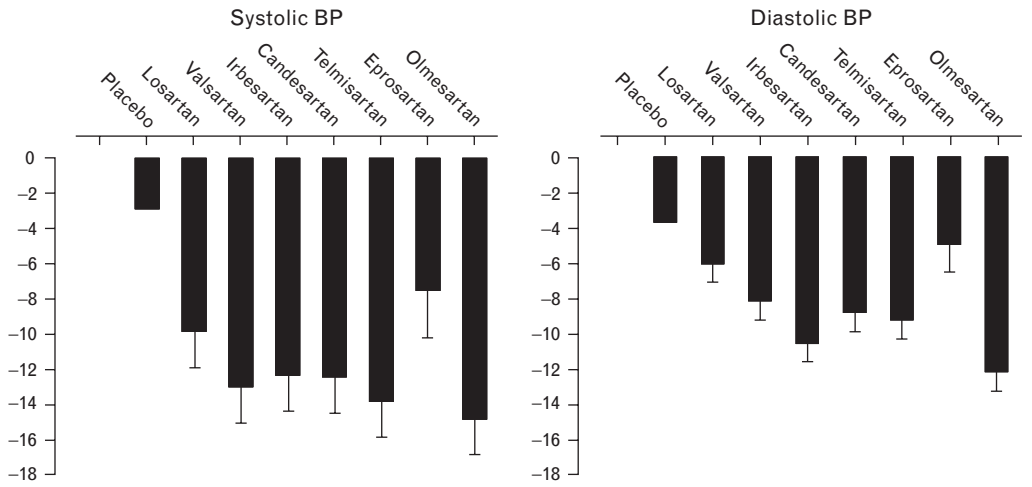
ARB, Angiotensin II AT_1 receptor antagonist; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 5 Values of *P* for the influence of drug and dose on the reduction of office and ambulatory 24-h blood pressure, day and night periods, and the last 4–6 h for the angiotensin II AT_1 receptor antagonists

	Initial BP	Drug	Dose
Office SBP	0.22	0.72	0.39
Office DBP	0.99	0.02	0.79
24-H SBP	0.27	0.03	0.05
24-H DBP	0.47	0.02	0.11
Day SBP	0.12	0.22	0.27
Day DBP	0.11	0.04	0.09
Night SBP	0.07	0.01	0.03
Night DBP	0.06	0.002	0.04
Last 4–6 h SBP	0.72	0.02	0.15
Last 4–6 h DBP	0.56	0.04	0.18

BP, Blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Fig. 2



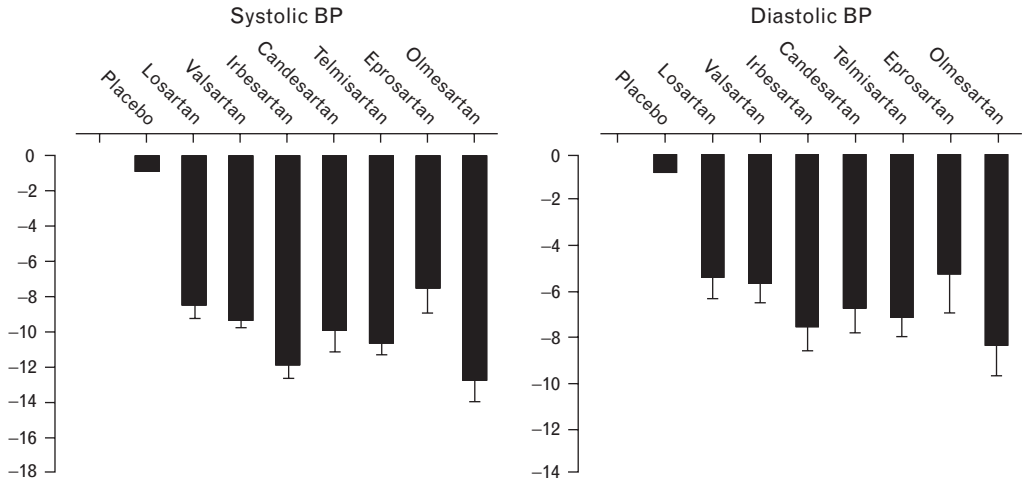
Reduction in the values of clinical blood pressure (BP) of each angiotensin II AT_1 receptor antagonist and placebo: systolic BP (left panel) and diastolic BP (right panel). Values are adjusted by initial BP values, dose, age and number of participants included in every cohort and are expressed as the average and the standard error. There is no statistical significance for systolic BP among the drugs ($P = 0.72$) or doses ($P = 0.39$). In the case of diastolic BP, however, statistical significance among the drugs ($P = 0.02$) is observed, but is not related to dosage ($P = 0.79$).

and in Figs 2–6. Although reductions in office and awake SBP were not significantly influenced by the specific drug or dose, both drug and dose influenced reductions in SBP of 24 h, at night, and during the last 4 h. Furthermore, the drug dosage influenced the possibility of extending the reduction to the nocturnal period. For DBP, the drug influenced the reductions in the office, 24 h, awake and sleep periods. In addition, dosage was also important for the nocturnal DBP reduction differences.

Impact of thiazide addition

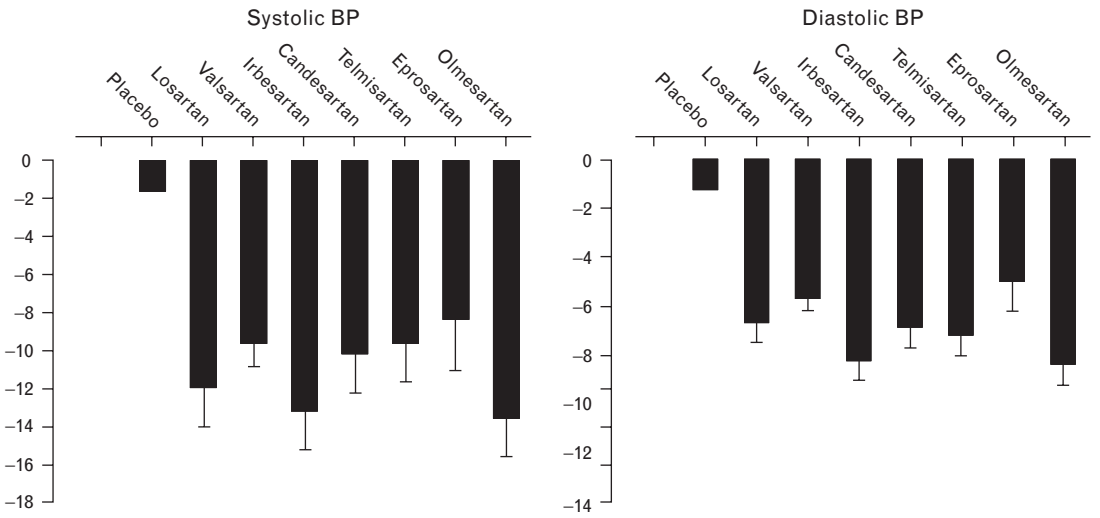
In 17 cohorts, a total of 1757 patients, the reduction in BP values was analysed when a thiazidic diuretic, usually hydrochlorothiazide 12.5 mg, was combined with the selected ARB. Only three studies used hydrochlorothiazide 25 mg. Considering the global BP reduction of the ARB and the ARB plus a diuretic, there was an additional significant reduction of 4.1 mmHg ($P < 0.001$) for the 24-h SBP and 3.8 mmHg ($P < 0.001$) for the clinic DBP. These

Fig. 3



Reduction in the values of blood pressure (BP) over 24 h of each angiotensin II AT_1 receptor antagonist and placebo: systolic BP (left panel) and diastolic BP (right panel). Values are adjusted by initial BP values, dose, age and number of participants included in every cohort and are expressed as the average and standard error. There is statistical significance for systolic BP and diastolic BP among the drugs ($P = 0.03$ and $P = 0.002$), respectively, but is not related to dosage ($P = 0.79$ and $P = 0.11$), respectively.

Fig. 4



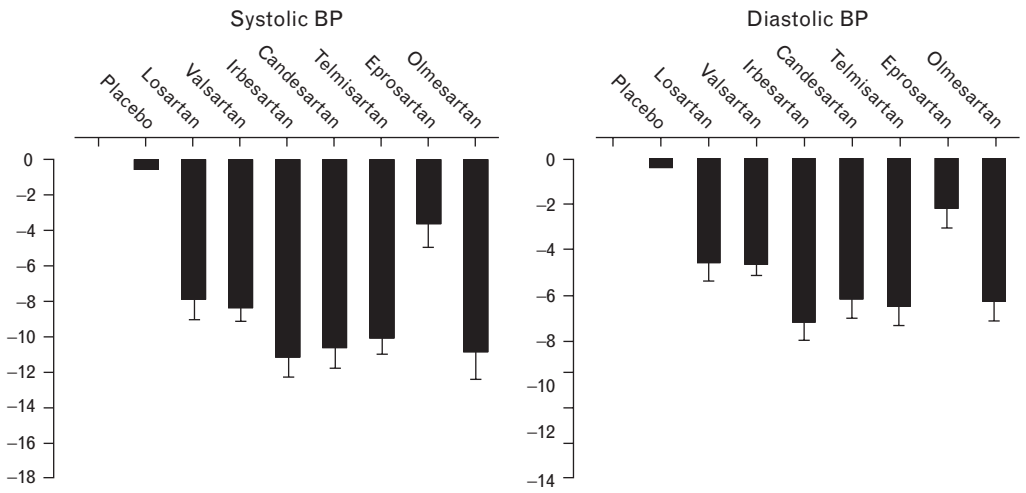
Reduction in the values of awake blood pressure (BP) of each angiotensin II AT_1 receptor antagonist and placebo: systolic BP (left panel) and diastolic BP (right panel). Values are adjusted by initial BP values, dose, age and number of participants included in every cohort and are expressed as the average and standard error. There is no statistical significance for systolic BP among the drugs ($P = 0.22$), or related to dosage ($P = 0.27$). In the case of diastolic BP, however, there is statistical significance among the drugs ($P = 0.04$), but not in relation to dosage ($P = 0.09$).

reductions were independent of the initial BP. The magnitude of the additional reduction was better seen in the average of ambulatory BP than it was in that for clinic BP. This can be explained because the difference in the BP value reduction is especially notable in the last 4–6 h of the interdose period, which indicates a longer duration of the antihypertensive activity (differences for SBP: activity 6.2 mmHg, $P = 0.006$; sleep 3.7 mmHg; $P = 0.06$; 4–6 h 7.0 mmHg, $P < 0.001$; differences for DBP: activity 4.4 mmHg, $P = 0.02$; sleep 4.1 mmHg, $P = 0.02$; 4–6 h 4.8 mmHg, $P < 0.001$).

Discussion

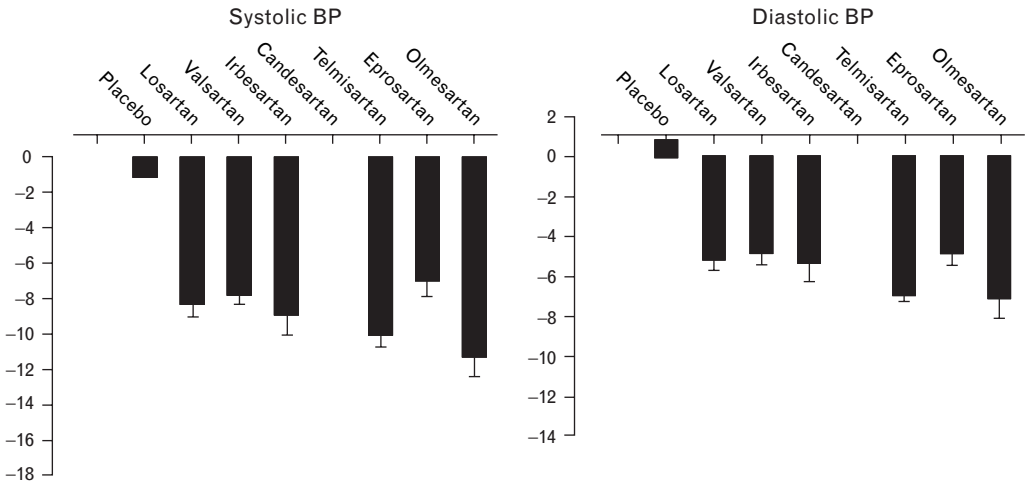
The present systematic review of the literature provides information about the characteristics of the antihypertensive activity of ARB, which seems to differ from the

Fig. 5



Reduction in the values of sleep blood pressure (BP) of each angiotensin II AT_1 receptor antagonist and placebo: systolic BP (left panel) and diastolic BP (right panel). Values are adjusted by initial BP values, dose, age and number of participants included in every cohort, and are expressed as the average and standard error. There is statistical significance for systolic BP and diastolic BP among the drugs ($P = 0.008$ and $P = 0.002$), respectively, and among the dosage ($P = 0.027$ and $P = 0.004$), respectively.

Fig. 6



Reduction in the values of blood pressure (BP) during the last 4 h of the interdose period of each angiotensin II AT_1 receptor antagonist and placebo: systolic BP (left panel) and diastolic BP (right panel). Values are adjusted by initial BP values, dose, age and number of participants included in every cohort, and are expressed as the average and standard error. There is statistical significance for systolic BP and diastolic BP among the drugs ($P = 0.02$ and $P = 0.04$), respectively, but is not related to dosage ($P = 0.15$ and $P = 0.18$), respectively.

activity observed with amlodipine. A calcium channel antagonist with reputed antihypertensive activity, amlodipine is able to reduce BP in a magnitude, which is more dependent on the dose and on the BP values before treatment than it was for ARB. When the possible influence of each ARB separately on the BP value reduction was assessed, it was observed that for DBP, the drug used was a determinant for the magnitude of the reduction. For SBP, however, the drug influenced mainly the duration of the antihypertensive activity. Similarly, among ARB, dose had a special influence on the duration of antihypertensive activity, independent of the drug used.

The present systematic review on the characteristics of ARB antihypertensive activity was not carried out in order to search for small differences in the antihypertensive activity of the specific ARB group, it tried to analyse the overall characteristics of antihypertensive activity. There are several contributions for the present study. It is the largest on the topic published up to now, including all the ARB marketed together and obtaining comparisons with two of the most widespread antihypertensive drugs, amlodipine and enalapril. This study has utilized the information contained in published studies in which the antihypertensive activity of one or more members of the group had been assessed through 24-h ABPM. The first step in study selection was performed using information from MEDLINE, assuming that almost all the studies had passed through a peer-review selection process and, therefore, methodologically met some minimum quality criteria. Although some studies were not randomized nor were they double blind, the fact that the main variable, ambulatory BP values, was collected without the observer's bias provides the reported information with validity. The analysis performed was adjusted using potential confounding variables; among these was the arterial pressure at the beginning of the study. The absence of initial BP values caused the elimination of up to 30 of the published studies from the analysis, almost 50% of those found in the review.

The data obtained for the present study hold great strength because the only studies used were those in which the BP reduction was assessed through 24-h ambulatory monitoring. Measuring BP 62–74 times during a 24-h monitoring period allows mean values to be obtained with less variability than those observed for clinic BP, in which the values are normally the mean of two, three, or at most, five measurements. This makes the antihypertensive response detected through ABPM more precise and reliable than clinic measurements. Moreover, ambulatory monitoring allows for antihypertensive activity measurements during different day and night periods under normal living conditions. These measurements are used to estimate the antihypertensive activity duration and the homogeneity in BP reduction. Those parameters that indicate the degree of homogenization of BP reduction, trough/peak ratio and smoothness index, were not analysed because they were calculated in only a few of the studies, and their values were widely dispersed.

Correlation coefficients between initial BP values and BP reduction during treatment were significantly higher for office than for ambulatory BP. Initial higher BP values, regression to the mean and additional reduction in BP

reactivity could explain the higher *r* values for office BP measurements. One thing stands out among all the features of the ARB antihypertensive activity: there exists a lower correlation between initial BP values and the magnitude of the reduction induced by drugs compared with amlodipine, a dihydropyridine with a potent direct vasodilatory activity that reduces calcium input in the smooth muscle fibers, or enalapril, an angiotensin-converting enzyme inhibitor with vasodilatory properties other than reducing angiotensin II activity.

The second feature of ARB is the scarce contribution of a dose increase, in the ranges used, to the antihypertensive activity reached during the patient activity period, in contrast to the antihypertensive activity of amlodipine and enalapril, which seems to increase with greater doses. As current trends are directed at the use of megadoses based on the good tolerance of the drug in search of a greater blockade of angiotensin II, whether or not doses higher than those used in these studies are capable of increasing the antihypertensive activity of the drugs should be investigated.

The last relevant aspect of the present study is the existence of differences in antihypertensive activity and duration among the drugs of the ARB group. Regardless of initial BP values, differences between drugs and between doses were observed. Whereas no differences were noticed between clinic SBP and activity SBP, the average of 24-h and night SBP differed in the function of the drug and its dose. Such a difference indicates that common drug administration in the first hours of the morning will achieve the adequate antihypertensive activity if using only certain drugs and at a high dosage. In the case of DBP, these differences and the role of dosage are even more evident. The antihypertensive activity, greater in certain drugs than in others, and the antihypertensive activity duration, also longer for some drugs than for others, are discussed in comparative studies and can be explained by means of pharmacokinetic and pharmacodynamic characteristics. It remains less commonly known that drug dosage not only increases antihypertensive activity, but also provokes longer activity duration, thus covering the night period. Whether administration at times different from those in the morning might modify this pattern is not certain, and it can not be analysed with the data from the present meta-analysis.

Finally, antihypertensive activity maintenance during the last 4 h of the interdose period seems to be dependent on the drug used, but much less on the dose. The absence of dose impact during the last 4 h, although influenced by the reduction during the nocturnal period, could be explained by two circumstances that are not mutually exclusive. First, that the impact of the dose for the temporal extension of the antihypertensive activity was inferior to the specific drug characteristics. A second explanation could be related to a greater variation in BP values during the last 4 h of the interdose interval, given the coincidence with the start of the activity and, therefore, with the beginning of the elevation of BP values. A greater variability may reduce the possibility of finding differences. In any case the use of high doses for certain drugs in order to achieve the greatest reduction in BP during the last hours of the interdose interval, would seem to be advisable.

In conclusion, from the information analysed in the present systematic review, some data of clinical relevance has been found. The antihypertensive activity of the ARB has a lower dependency on BP values before treatment compared with amlodipine or enalapril. The ARB differ significantly not only in their antihypertensive activity but also in the time duration. The duration also depends on the dose administered. The clinical importance of these differences to hypertension-induced morbidity and mortality is difficult to assess.

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