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Sustained 24-hour blockade of the renin-angiotensin system: A high dose of a long-acting blocker is as effective as a lower dose combined with an angiotensin-converting enzyme inhibitor

THESE

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Résumé en français

Jusqu'alors, il n'avait jamais été formellement démontré qu'une forte dose d'un antagoniste de l'angiotensine II à longue durée d'action pouvait être aussi efficace sur le blocage du système rénine-angiotensine que l'association d'un inhibiteur de l'enzyme de conversion avec le même antagoniste de l'angiotensine II à des doses plus faibles. Dans cette étude randomisée en double aveugle, nous avons étudié le blocage du système rénine-angiotensine obtenu avec trois doses d'olmesartan medoxomil (20, 40 et 80 mg) chez 30 volontaires sains que nous avons comparé au blocage obtenu par du lisinopril (20 mg), seul ou associé à de l'olmesartan medoxomil (20 et 40 mg). L'étude s'est déroulée en deux phases selon un design par crossover. A deux reprises, chaque volontaire à reçu durant une semaine l'un des six traitements possibles. Un intervalle d'une semaine a été respecté entre les deux phases (période de washout). L'objectif principal était d'étudier, 24 heures après la dernière dose, le blocage de l'élévation de la pression systolique en réponse à l'administration d'angiotensine I. Ce blocage était de 58% ± 19% (moyenne ± déviation standard) avec 20 mg de lisinopril, de 58% ± 11% avec 20 mg d'olmesartan medoxomil, de 62% ±16% avec 40 mg d'olmesartan medoxomil, et de 76% ± 12% avec la plus forte dose d'olmesartan medoxomil (80 mg) (P= .016 versus 20 mg de lisinopril et P=.0015 versus 20 mg d'olmesartan medoxomil). Le blocage était de 80% ±22% avec 20 mg de lisinopril associé à 20 mg d'olmesartan medoxomil et de 83% ± 9% avec 20 mg de lisinopril associé à 40 mg d'olmesartan medoxomil (P= .3 versus 80 mg d'olmesartan medoxomil). Ces résultats montrent, que chez les volontaires sains, une dose suffisamment élevée d'olmesartan medoxomil peut induire un blocage à 24 heures quasi complet de l'élévation de la pression artérielle en réponse à l'administration d'angiotensine I. De même, en terme de blocage de l'effet vasculaire de l'angiotensine I, une dose suffisamment élevée d'un antagoniste de l'angiotensine II de longue durée d'action est tout aussi efficace que ce même antagoniste à des doses plus faibles associé avec à un inhibiteur de l'enzyme de conversion.

Sustained 24-hour blockade of the renin-angiotensin system: A high dose of a long-acting blocker is as effective as a lower dose combined with an angiotensin-converting enzyme inhibitor

Whether a higher dose of a long-acting angiotensin II receptor blocker (ARB) can provide as much blockade of the renin-angiotensin system over a 24-hour period as the combination of an angiotensin-converting enzyme inhibitor and a lower dose of ARB has not been formally demonstrated so far. In this randomized double-blind study we investigated renin-angiotensin system blockade obtained with 3 doses of olmesartan medoxomil (20, 40, and 80 mg every day) in 30 normal subjects and compared it with that obtained with lisinopril alone (20 mg every day) or combined with olmesartan medoxomil (20 or 40 mg). Each subject received 2 dose regimens for 1 week according to a crossover design with a 1-week washout period between doses. The primary endpoint was the degree of blockade of the systolic blood pressure response to angiotensin I 24 hours after the last dose after 1 week of administration. At trough, the systolic blood pressure response to exogenous angiotensin I was 58% ± 19% with 20 mg lisinopril (mean ± SD), 58% ± 11% with 20 mg olmesartan medoxomil, 62% ± 16% with 40 mg olmesartan medoxomil, and 76% ± 12% with the highest dose of olmesartan medoxomil (80 mg) ($P = .016$ versus 20 mg lisinopril and $P = .0015$ versus 20 mg olmesartan medoxomil). With the combinations, blockade was 80% ± 22% with 20 mg lisinopril plus 20 mg olmesartan medoxomil and 83% ± 9% with 20 mg lisinopril plus 40 mg olmesartan medoxomil ($P = .3$ versus 80 mg olmesartan medoxomil alone). These data demonstrate that a higher dose of the long-acting ARB olmesartan medoxomil can produce an almost complete 24-hour blockade of the blood pressure response to exogenous angiotensin in normal subjects. Hence, a higher dose of a long-acting ARB is as effective as a lower dose of the same compound combined with an angiotensin-converting enzyme inhibitor in terms of blockade of the vascular effects of angiotensin. (Clin Pharmacol Ther 2005;78:501-7.)

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Blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) represents an effective therapeutic approach to treat hypertension and congestive heart failure and to prevent the progression of diabetic and nondiabetic renal disease.[1] This has established angiotensin II as a key factor contributing to blood pressure increase and multiple organ damage. As a consequence, blockade of the synthesis or action of angiotensin II around the clock becomes a clear therapeutic goal, particularly because complete blockade of the RAS does not seem to elicit untoward effects. In recent years several studies have suggested that a greater and more sustained blockade of the RAS could be obtained with the combination of an ACEI and an ARB and that the ACEI-ARB combination may provide additional clinical benefits when compared with either drug alone.[2-6] This hypothesis has been supported by the recent results of trials con-

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ducted in patients with diabetic and nondiabetic nephropathies and in patients with heart failure.[7-9]

Early studies have demonstrated that it is very difficult to obtain a complete 24-hour blockade of the RAS with an ACEI because angiotensin II can be generated by other enzymatic pathways and also because with an ACEI, as a result of the reactive increase in plasma renin activity, angiotensin II is produced as soon as some angiotensin-converting enzyme (ACE) activity reappears.[10-13] We have also demonstrated previously that several ARBs do not induce a complete 24-hour blockade of the receptor at their recommended doses in healthy subjects.[14,15] Hence the combination with an ACEI is indeed expected to increase and prolong the blockade of the RAS because both compounds provide only a partial blockade per se. However, we have also shown recently that an increase in the dose of the ARB or a twice-daily administration of some ARBs with a shorter duration of action could produce as much blockade of the RAS as an ACEI-ARB combination.[16] Thus a potent, long-acting ARB could conceivably be as effective as an ACEI-ARB combination to induce a sustained 24-hour blockade of the RAS, provided that the dose of the drug is chosen and characterized appropriately. Such a compound would of course have the advantages of simplifying the treatment (only 1 drug to administer) and avoiding the potential side effects of ACEIs.

In this study, we investigated the blockade of the RAS obtained with 3 doses of olmesartan medoxomil, an ARB with a relatively long half-life, in normotensive subjects and compared it with that obtained with lisinopril alone or combined with a lower dose of olmesartan medoxomil.

METHODS

Subjects. Thirty normotensive male subjects were enrolled in this study (26 white subjects and 4 nonwhite subjects). The mean age was 23.9 years (range, 20-35 years), and the mean body mass index was 21.6 kg/m^2 (range, 19.0-26.0 kg/m^2).

All subjects were considered to be healthy on the basis of medical history, physical examination, routine blood and urine analyses, and an electrocardiogram. None had a family history of hypertension. The study protocol was approved by our institutional review committee. Written consent was obtained from each volunteer after the nature, purpose, and potential risks of the study were explained.

Study design. In this double-blind crossover study the volunteers were distributed into 6 groups, and within each group, each subject was randomized to receive 2 treatments for 1 week, separated by a 4-week washout period. During the last 3 days of each treatment, subjects received a 100-mmol sodium diet at the hospital. In each treatment phase, one of the following regimens was randomly assigned: 20 mg lisinopril every day, 20 mg olmesartan medoxomil every day, 40 mg olmesartan medoxomil every day, 80 mg olmesartan medoxomil every day, 20 mg olmesartan medoxomil plus 20 mg lisinopril every day, and 40 mg olmesartan medoxomil plus 20 mg lisinopril every day. To maintain double-blindness, placebo tablets were given to the subjects randomized to a single therapy. Blockade of the RAS was assessed at 0 and 4 hours on day 1 without drug intake to determine the baseline value and again at 0 and 4 hours on the last day of treatment (day 8). On each investigational day, volunteers were asked to come to our research facility after an overnight fast. They were comfortably situated in a supine position, and a venous catheter was placed in each forearm, one for blood sampling and the other for the intravenous injection of angiotensin I (Clinalfa, Läufelfingen, Switzerland). At each time point (0 and 4 hours), the short-term changes in blood pressure induced by the administration of exogenous angiotensin I were measured by photoplethysmography at the finger as described previously.[17] The doses of angiotensin I were defined for each subject on day 1 to increase systolic blood pressure by at least 25 mm Hg. Thus the doses ranged between 20 and 60 ng/kg depending on the subjects. Thereafter the same dose of angiotensin I was readministered on day 1 at 4 hours and on day 8 at 0 and 4 hours. In addition, blood was taken to measure plasma renin activity and plasma angiotensin II levels before the administration of exogenous angiotensin I. During the entire study, the volunteers were asked to come back every morning to receive the drugs under medical supervision.

Blood pressure measurement and hormonal measurements. Blood pressure response to exogenous angiotensin I was monitored noninvasively by photoplethysmography at the finger (Finapress; Ohmeda, Englewood, Conn). The photoplethysmograph was calibrated every day on the basis of blood pressure measured at the arm. The system has been validated previously.[18] Blood pressure was also measured with a standard sphygmomanometer at trough before administration of any dose of exogenous angiotensin on days 1 and 8 to monitor the sustained effects of the drug regimens on blood pressure. Blood was drawn at the same time of day in each group to standardize the measurements. Plasma renin activity was measured by use of a radioimmunologic microassay based on angiotensin I trapping by antibody. Angiotensin II

Table I. Changes in trough supine blood pressure observed after 1 week of drug administration

	Dose (mg)	*Baseline blood pressure (mm Hg)*	*Change in systolic blood pressure (mm Hg)**	*P value*	*Change in diastolic blood pressure (mm Hg)**	*P value*
Lisinopril	20	117/68	−2.9 ± 5.8	.15	−1.7 ± 5.8	.38
Olmesartan medoxomil	20	114/66	−5.6 ± 6.9	.031	−3.0 ± 4.2	.051
Olmesartan medoxomil	40	113/65	−6.2 ± 5.6	.006	−5.6 ± 5.1	.007
Olmesartan medoxomil	80	117/67	−5.9 ± 5.8	.010	−2.8 ± 4.9	.103
Olmesartan medoxomil + 20 mg lisinopril	20	115/67	−10.3 ± 8.3	.003	−5.6 ± 8.2	.060
Olmesartan medoxomil + 20 mg lisinopril	40	116/66	−6.7 ± 7.2	.016	−5.1 ± 5.1	.011

All values are presented as mean ± SD. Baseline values were measured on day 1 at time 0.
*Blood pressure was measured with a conventional sphygmomanometer.

concentration was determined by use of a monoclonal antibody binding assay.[19]

Statistical analysis. All results are presented as mean ± SD unless otherwise specified. As mentioned previously, the primary endpoint was the systolic blood pressure response to exogenous angiotensin I at 24 hours. All analyses were performed in a double-blind manner. Our study was powered to conclude on a difference in blockade greater than 15%. One-way ANOVA was performed, followed by either paired or unpaired *t* tests by use of GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, Calif). $P < .05$ was considered to be statistically significant.

RESULTS

All doses of olmesartan medoxomil and lisinopril were well tolerated. Compliance to drug treatment was 100%. In the 6 groups of subjects, the median 24-hour urinary sodium excretion on day 1 of the first treatment phase ranged between 106 and 137 mmol/24 hours, with no significant difference between the groups. On the first day of the second treatment phase, 24-hour urinary sodium excretion was slightly higher, with a median for each group ranging between 109 and 160 mmol/24 hours, suggesting that the compliance to the diet decreased from the first to the second phase. Again, no statistical difference between the groups was observed. One subject had to be withdrawn and replaced because mild alterations of hepatic test results developed with the administration of olmesartan medoxomil in this subject. These alterations normalized after interruption of olmesartan medoxomil. Three months later, liver function was normal and no diagnosis of viral hepatitis could be retained. This suggests that the alterations were probably due to the administration of olmesartan medoxomil.

As shown in Table I, after 1 week of administration, a significant decrease in systolic blood pressure was observed with all doses except for 20 mg lisinopril every day. The changes in diastolic blood pressure were less consistent, with significant decreases observed only with 40 mg olmesartan medoxomil and the combination of 40 mg olmesartan medoxomil and 20 mg lisinopril. The changes in systolic and diastolic blood pressure induced by the 2 olmesartan medoxomil–lisinopril combinations were not different from those obtained with the 3 doses of olmesartan medoxomil alone.

After 1 week of administration, all treatment schedules induced a marked blockade (>80%) of the blood pressure response to exogenous angiotensin I 4 hours after drug intake, and there was no significant difference between the doses (Fig 1). In contrast, the blockade of the RAS obtained at trough (time 0) on day 8 differed depending on the dose administered, as shown in Fig 1. Thus the systolic blood pressure response to exogenous angiotensin I was blocked by 58% ± 19% with 20 mg lisinopril, 58% ± 11% with 20 mg olmesartan medoxomil, 62% ± 16% with 40 mg olmesartan medoxomil, and 76% ± 12% with the highest dose of olmesartan medoxomil (80 mg). At the same time point, the response to angiotensin I was blunted by 80% ± 22% with 20 mg olmesartan medoxomil plus 20 mg lisinopril and by 83% ± 9% with 40 mg olmesartan medoxomil plus 20 mg lisinopril. The combinations provided significantly more blockade than either drug alone but were not greater than that with the highest dose of olmesartan medoxomil (80 mg every day).

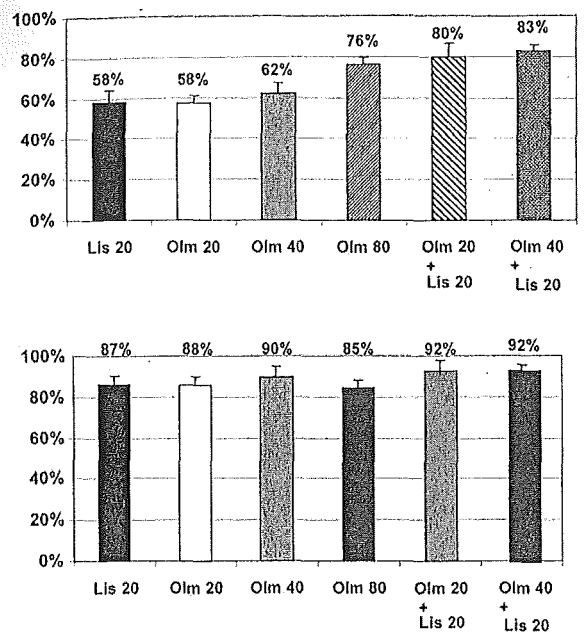

Fig 1. Summary of blockade of systolic blood pressure (SBP) response to exogenous angiotensin I (Ang I), after 1 week of treatment, at trough (ie, before dosing on day 8) (*upper panel*) and 4 hours after dosing on day 8 (*lower panel*) in different study groups. Data are presented as mean ± SD. At trough (*upper panel*), 80 mg olmesartan medoxomil (Olm) (P = .016), 20 mg olmesartan medoxomil plus 20 mg lisinopril (Lis) (P = .0028), and 40 mg olmesartan medoxomil plus 20 mg lisinopril (P = .0123) were significantly different from 20 mg lisinopril. In addition, 80 mg olmesartan medoxomil (P = .0015), 20 mg olmesartan medoxomil plus 20 mg lisinopril (P = .041), and 40 mg olmesartan medoxomil plus 20 mg lisinopril (P = .001) were also significantly different from 20 mg olmesartan medoxomil. Finally, 40 mg olmesartan medoxomil plus 20 mg lisinopril (P = .008) and 80 mg olmesartan medoxomil (P = .05) were significantly different from 40 mg olmesartan medoxomil. The other comparisons between groups were not significant. At 4 hours (*lower panel*), all groups were comparable statistically.

Table II shows the changes in plasma renin activity and plasma angiotensin II levels induced by the various dose schedules in our subjects. As expected, increasing the dose of olmesartan medoxomil induced a dose-dependent increase in plasma renin activity at trough and comparable changes at 4 hours. As far as renin is concerned, the olmesartan medoxomil–lisinopril combinations were superior to 20 mg lisinopril and 20 mg olmesartan medoxomil but were not different from the 40- and 80-mg doses of olmesartan medoxomil. As expected, plasma angiotensin II levels were reduced under ACE inhibition and were significantly lower with the olmesartan medoxomil–lisinopril combinations than with olmesartan medoxomil alone on day 8. The statistical differences between the groups are shown in Table III.

DISCUSSION

Taken together, the results of this study demonstrate that the long-acting ARB olmesartan medoxomil can produce an almost complete 24-hour blockade of the RAS at the dose of 80 mg once daily for 1 week in normotensive subjects. Combining a lower dose of the same ARB with an ACEI does not provide a greater blockade of the system at least in terms of inhibition of the vasoconstrictor effects of angiotensin. Hence the use of a higher dose of a well-tolerated angiotensin II antagonist may be a good alternative to the ACEI–angiotensin II antagonist combination.

Given that there exists extensive evidence that angiotensin II may exert detrimental vascular effects beyond raising blood pressure,[20,21] it would seem logical to pursue as a treatment target complete blockade of the RAS around the clock. At their recommended doses, few of the angiotensin II receptor antagonists, if any, have been found to induce a complete blockade of the RAS around the clock. Yet in an earlier study we have provided evidence that this can be achieved with losartan alone administered at a dose of 100 mg twice a day.[16] The present results demonstrate that the same goal can be achieved with olmesartan medoxomil administered only once per 24 hours. Whether marked blockade of the RAS at trough versus incomplete blockade indeed translates into better outcome in hypertensive patients still needs to be further investigated but a priori seems reasonable to expect. Thus the outcome of the VALUE (valsartan antihypertensive long-term use evaluation) trial would perhaps have been different if valsartan had been given at higher doses and possibly twice a day as in the ValHeft (valsartan heart failure trial) study.[22,23]

Blockade of the RAS for the duration of 24 hours can be achieved very well by the combination of relatively low doses of an ARB with an ACEI.[2-4] The potential limitation with the combination lies in the side effects of the ACEIs. In contrast to ACEIs, ARBs have not exhibited any typical class side effects thus far.[24] Thus even high doses of ARBs, which provide sustained blockade and are hoped to enhance organ protection, will probably do this without causing any untoward effects. This unique combination of substantial and sustained efficacy with a favorable tolerability profile

Table II. Plasma renin activity and plasma angiotensin II levels in different study groups

	Plasma renin activity (ng · mL^{-1} · h^{-1})				*Plasma angiotensin II levels (fmol/mL)*			
	Day 1 (baseline)		*Day 8*		*Day 1 (baseline)*		*Day 8*	
Treatment	*0 h*	*4 h*	*0 h (trough)*	*4 h (peak)*	*0 h*	*4 h*	*0 h (trough)*	*4 h (peak)*
Lis 20	1.5 ± 1.0	1.1 ± 1.2	9.3 ± 6.6	21.7 ± 15.4	3.8 ± 0.9	2.6 ± 0.8	3.5 ± 1.7	1.2 ± 1.0
Olm 20	1.5 ± 0.5	1.5 ± 0.7	4.5 ± 6.8	13.7 ± 16.9	5.3 ± 1.7	4.8 ± 2.8	26.8 ± 13.2	89 ± 72
Olm 40	1.5 ± 1.0	1.9 ± 1.2	11.0 ± 6.6	26.8 ± 15.4	3.8 ± 1.3	3.3 ± 1.8	54.3 ± 31.2	128 ± 116
Olm 80	1.4 ± 0.5	1.4 ± 0.7	14.6 ± 6.8	27.0 ± 16.9	3.3 ± 2.5	3.7 ± 1.9	69.9 ± 55.4	144 ± 109
Olm 20 + Lis 20	1.3 ± 0.8	1.4 ± 0.8	19.1 ± 18.6	33.6 ± 32.9	2.7 ± 1.2	3.6 ± 1.7	8.0 ± 5.8	3.2 ± 1.6
Olm 20 + Lis 20	1.3 ± 0.4	1.6 ± 0.7	22.4 ± 15.7	30.6 ± 26.0	3.8 ± 1.4	4.2 ± 2.3	8.4 ± 3.2	2.5 ± 1.2

Values are given as mean ± SD.
Lis, Lisinopril; Olm, olmesartan medoxomil.

Table III. Statistical differences in plasma renin activity and plasma angiotensin II levels in different groups

Treatment	*Lis 20*	*Olm 20*	*Olm 40*	*Olm 80*	*Olm 20 + Lis 20*	*Olm 40 + Lis 20*
Plasma renin activity (*P* value between different study groups at 1 wk [0 h/4 h])						
Lis 20	—	.07/.18	.24/.60	.13/.98	.07/.34	.048/.31
Olm 20		—	.042/.07	.008/.23	.04/.10	.005/.09
Olm 40			—	.30/.53	.11/.46	.09/.65
Olm 80				—	.39/.08	.21/.38
Olm 20 + Lis 20					—	.74/.88
Olm 40 + Lis 20						—
Plasma angiotensin II levels (*P* value between different study groups at 1 wk [0 h/4 h])						
Lis 20	—	.001/.003	.001/.007	.005/.002	.054/.017	.001/.016
Olm 20		—	.041/.45	.052/.22	.004/.004	.001/.004
Olm 40			—	.43/.53	.001/.007	.001/.007
Olm 80				—	.006/.002	.008/.002
Olm 20 + Lis 20					—	.81/.32
Olm 40 + Lis 20						—

renders this treatment very attractive for potential long-term organ protection. As shown in our study, the main difference between a high dose of an angiotensin II receptor antagonist and a combination of an ACEI and an ARB is the circulating level of angiotensin II. In the former situation, angiotensin II levels are very much increased, whereas in the latter situation, angiotensin II levels are moderately increased. Whether these differences in circulating angiotensin II have a clinical impact is difficult to appreciate. Indeed, high angiotensin II levels may stimulate the unblocked angiotensin AT_2 receptors. However, the clinical impact of long-term stimulation of AT_2 receptors is not known. Similarly, one could argue that other pharmacologic properties of ACE inhibition such as bradykinin generation may have some additive value in favor of the combination, but this has not been formerly demonstrated either. Of note, significant decreases in systolic blood pressure were observed in our otherwise normotensive subjects with the administration of olmesartan medoxomil alone or in association with the ACEI, whereas lisinopril alone at the dose of 20 mg every day had no effect on blood pressure. The changes in blood pressure can be explained by the fact that subjects were moderately salt-depleted because they received a diet of 100-mmol sodium per day for the 3 days preceding each investigation with exogenous angiotensin II.

As discussed in previous reports, a possible limitation of our observation is that it has been obtained in normotensive healthy subjects receiving normal

salt intake (ie, with a reactive RAS).[16] Hence our observation may not apply to all types of hypertensive patients. Thus patients with low renin activity (elderly or hypertensive patients receiving a β-blocker) may not necessarily benefit from a higher dose of ARB, but whether these patients would benefit from a combination of ACEI and ARB is also questionable. In low-renin conditions, combined blockade of the RAS with 150 mg irbesartan and 20 mg fosinopril appeared to be superior to receptor blockade alone with 300 mg irbesartan, but whether a higher dose of irbesartan would be as effective as the combination has not been evaluated.[25] Moreover, it is interesting to note that, besides heart failure, the clinical interest of combining an ACEI with an ARB has been demonstrated mainly in patients with nondiabetic or diabetic nephropathy, the latter often being considered to have a low intrinsic activity of the RAS.[6-9,26] In the same groups of patients, high doses of ARBs or ACEIs have been reported to be more effective in reducing proteinuria or providing renal protection than lower doses or as effective as the ACEI-ARB combination.[27-30]

In conclusion, several large clinical trials investigating the ability of ARBs to protect hypertensive patients against target organ damage have now repeatedly shown that the highest doses were the most effective[31-34] and that there may be a potential for more aggressive treatment. These studies have also suggested that there may be benefits of blocking the effects of angiotensin II beyond blood pressure control.[34] Rather complete blockade of the RAS around the clock can be achieved by combining an ACEI and an ARB or with a higher dose of a long-acting ARB, as demonstrated in this study with olmesartan medoxomil. However, monotherapy with an ARB alone as opposed to the combination has the advantages of an absence of side effects and probably better compliance. On the basis of recent evidence from several trials, it is likely that more complete blockade of the RAS than hitherto used may become the standard for improved vascular, cardiac, and renal protection. Clinical studies with various ARBs are now ongoing to demonstrate that higher doses can indeed fulfill this expectancy.

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