

# Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



*Learn and Live*<sup>SM</sup>

## **Chronotherapy With the Angiotensin-Converting Enzyme Inhibitor Ramipril in Essential Hypertension: Improved Blood Pressure Control With Bedtime Dosing**

Ramón C. Hermida and Diana E. Ayala

*Hypertension* 2009;54;40-46; originally published online May 11, 2009;

DOI: 10.1161/HYPERTENSIONAHA.109.130203

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2009 American Heart Association. All rights reserved. Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/cgi/content/full/54/1/40>

Data Supplement (unedited) at:

<http://hyper.ahajournals.org/cgi/content/full/HYPERTENSIONAHA.109.130203/DC1>

Subscriptions: Information about subscribing to Hypertension is online at  
<http://hyper.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:  
[journalpermissions@lww.com](mailto:journalpermissions@lww.com)

Reprints: Information about reprints can be found online at  
<http://www.lww.com/reprints>

## Chronotherapy With the Angiotensin-Converting Enzyme Inhibitor Ramipril in Essential Hypertension Improved Blood Pressure Control With Bedtime Dosing

Ramón C. Hermida, Diana E. Ayala

**Abstract**—Clinical studies have demonstrated a different effect on blood pressure of some angiotensin-converting enzyme inhibitors when administered in the morning versus the evening. Their administration at bedtime resulted in a higher effect on nighttime blood pressure as compared with morning dosing. This study investigated the administration time-dependent effects of ramipril on ambulatory blood pressure. We studied 115 untreated hypertensive patients,  $46.7 \pm 11.2$  years of age, randomly assigned to receive ramipril (5 mg/d) as a monotherapy either on awakening or at bedtime. Blood pressure was measured for 48 hours before and after 6 weeks of treatment. The blood pressure reduction during diurnal activity was similar for both treatment times. Bedtime administration of ramipril, however, was significantly more efficient than morning administration in reducing asleep blood pressure. The awake:asleep blood pressure ratio was decreased after ramipril on awakening but significantly increased toward a more dipping pattern after bedtime dosing. The proportion of patients with controlled ambulatory blood pressure increased from 43% to 65% ( $P=0.019$ ) with bedtime treatment. Nocturnal blood pressure regulation is significantly better achieved at bedtime as compared with morning administration of ramipril, without any loss in efficacy during diurnal active hours. This might be clinically important, because nighttime blood pressure has been shown to be a more relevant marker of cardiovascular risk than diurnal mean values. The change in the dose-response curve, increased proportion of controlled patients, and improved efficacy on nighttime blood pressure with administration of ramipril at bedtime should be taken into account when prescribing this angiotensin-converting enzyme inhibitor for treatment of essential hypertension. (*Hypertension*. 2009;54:40-46.)

**Key Words:** ramipril ■ essential hypertension ■ ambulatory blood pressure monitoring ■ chronotherapy ■ dipper ■ nondipper ■ angiotensin-converting enzyme inhibitors

Several attributes of the cardiovascular system, including blood pressure (BP) and heart rate (HR), are characterized by predictable changes during the 24 hours for the most part in synchrony with the rest-activity cycle.<sup>1</sup> Because the main steps in the mechanisms regulating BP are circadian-stage dependent,<sup>2</sup> it is not surprising that antihypertensive medications may display a circadian time dependency in their pharmacokinetics and pharmacodynamics.<sup>3</sup>

Clinical studies have consistently documented differences in BP-lowering efficacy, duration of action, and effects on the circadian BP pattern depending on the administration time of medications interacting with the renin-angiotensin-aldosterone system.<sup>3</sup> Independent trials have demonstrated a different effect of several angiotensin-converting enzyme (ACE) inhibitors when dosed in the morning versus the evening.<sup>3,4</sup> A small trial of 33 patients with essential hypertension has shown that a low dose of 2.5 mg/d of ramipril more effectively reduced daytime BP when it was administered in

the morning and more effectively reduced nighttime BP when it was administered in the evening.<sup>5</sup> Results were thought to be attributed to a <24-hour duration of action of this ACE inhibitor when administered at such a low dose. Clinical studies relying on ambulatory BP monitoring (ABPM) have shown, however, that higher doses of ramipril (5 to 10 mg/d) might provide full 24-hour coverage.<sup>6</sup>

Accordingly, this prospective trial was designed to compare, using BP data collected by 48-hour ABPM, the antihypertensive efficacy of the ACE inhibitor ramipril when ingested as a monotherapy either after awakening or at bedtime for a 6-week duration in previously untreated patients with uncomplicated essential hypertension.

### Methods

#### Inclusion and Exclusion Criteria

Inclusion criteria were age  $\geq 18$  years and a diagnosis of previously untreated grade 1 or 2 uncomplicated essential hypertension accord-

Received February 3, 2009; first decision February 22, 2009; revision accepted April 14, 2009.

From the Bioengineering and Chronobiology Laboratories, University of Vigo, Campus Universitario, Vigo, 36200 Spain.

This trial has been registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (identifier NCT00473174).

Correspondence to Ramón C. Hermida, Bioengineering and Chronobiology Laboratories, ETSI Telecomunicación, Campus Universitario, VIGO (Pontevedra) 36200, Spain. E-mail [rhermida@uvigo.es](mailto:rhermida@uvigo.es)

© 2009 American Heart Association, Inc.

*Hypertension* is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.109.130203

ing to the European Society of Hypertension-European Society of Cardiology guidelines,<sup>7</sup> as determined by repeated (within the 3 months before recruitment) conventional clinic BP measurements (systolic BP [SBP]: 140 to 179 mm Hg and/or diastolic BP [DBP]: 90 to 109 mm Hg) and corroborated by 48-hour ABPM at the time of recruitment. The diagnosis of hypertension based on 48-hour ABPM required an awake BP mean of  $\geq 135/85$  mm Hg or an asleep BP mean of  $\geq 120/70$  mm Hg.<sup>7</sup>

Pregnant women, shift workers, heavy drinkers (alcohol intake  $>80$  g/d), heavy smokers ( $>20$  cigarettes per day), and heavy exercisers were excluded, as were individuals with severe arterial hypertension (grade 3, BP  $\geq 180/110$  mm Hg), type 1 diabetes mellitus, or secondary arterial hypertension and cardiovascular disorders, including concomitant unstable angina pectoris, heart failure, stroke, life threatening arrhythmia, nephropathy, retinopathy, or previous (within the last year) myocardial infarction or coronary revascularization.

### Study Design

This was a prospective, randomized, open-label, parallel-group, blinded end point multicenter clinical trial. During the inclusion period (2007–2008) we screened 139 patients (all with a daytime active and nocturnal resting routine) and identified 120 who met the inclusion/exclusion criteria. Among these, 115 (52 men and 63 women),  $46.7 \pm 11.2$  years of age, completed the study and provided all of the required information for this trial. The ethics committee of clinical research approved the study. All of the subjects gave written informed consent.

Patients were randomly assigned (using an allocation table produced by a computerized random-number generator) to 1 of 2 groups specific to the time of day, either in the morning on awakening or at bedtime, of once-daily ramipril treatment (5 mg/d, the initial recommended dose in Spain) for 6 weeks. The demographic and analytic characteristics of the 2 groups of participants at baseline and after the 6 weeks of treatment are described in the online data supplement (Table S1, available at <http://hyper.ahajournals.org>).

At each of the 2 visits to the medical setting, before and after 6 weeks of therapy, respectively, 6 clinic BP measurements were obtained, after the patient had rested in a seated position for  $\geq 10$  minutes, using a validated automatic oscillometric device (HEM-705IT, Omron Health Care Inc). Blood samples were obtained during both clinic visits from the antecubital vein between 8 AM and 9 AM after nocturnal fasting.

### ABPM Assessment

The SBP, DBP, and HR of each participant were automatically measured every 20 minutes from 7 AM to 11 PM and every 30 minutes during the night for 48 consecutive hours, before and after timed therapy, with a properly calibrated SpaceLabs 90207 device (SpaceLabs Inc). Participants were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the 2 days of ABPM and to avoid daytime napping.

BP series were not considered valid for analysis if  $>30\%$  of the measurements were missing, if data were missing for an interval of  $>2$  hours, if data were obtained while patients had an irregular rest-activity schedule during the 2 days of monitoring, or if the nighttime sleep period was  $<6$  hours or  $>12$  hours during ABPM. Protocol-correct data series were collected at baseline and after treatment from 115 patients and, therefore, were included in this efficacy study. Baseline BP profiles of 5 additional patients (2 originally assigned to ramipril on awakening and 3 to ramipril at bedtime) were eliminated from this efficacy trial because of lack of follow-up: the patients from which they were derived either failed to return for the second ABPM after treatment (3 patients) or they withdrew from the trial because of adverse effects (1 on awakening dosing: paresthesia; 1 on bedtime dosing: edema).

### Actigraphy

All of the participants wore an Actigraph (Mini-Motion-Logger, Ambulatory Monitoring Inc) on the dominant wrist to monitor

physical activity every minute during both ABPM sessions. This compact (approximately half the size of a wristwatch) device works as an accelerometer. We synchronized the internal clocks of the Actigraph and the ABPM device through their respective interfaces using the same computer. The actigraphy data were used to determine the beginning and end of daytime activity and nocturnal sleep so that the awake and asleep BP means for each patient could be determined with accuracy.

### Statistical Methods

Assuming an SD of 8.0 mm Hg for ABPM and with 55 subjects per timed-treatment arm, the study could have 90% power to show as significant at the 95% level differences in efficacy of 5 mm Hg in daytime or nighttime BP means between treatment groups.

Each individual's clock hour BP and HR values were first referenced to hours after awakening from nocturnal sleep, based on data obtained by wrist actigraphy. This transformation avoided the introduction of bias because of slight differences among subjects in their sleep/activity routine. To correct for measurement errors and outliers, BP and HR were edited according to conventional criteria.<sup>8</sup> Thus, readings of SBP  $>250$  or  $<70$  mm Hg, DBP  $>150$  or  $<40$  mm Hg, and pulse pressure (difference between SBP and DBP)  $>150$  or  $<20$  mm Hg were automatically discarded.

Hourly BP means obtained before and after treatment for each group were compared by paired *t* test corrected for multiple testing. In so doing, the level of significance was established at  $P \leq 0.002$ , after dividing the usual level of 0.05 by the number of tests (24, 1 for each hourly mean) done on the same variable. Both the absolute and the relative changes from baseline in awake, asleep, and 24-hour BP means, as well as in the awake:asleep BP ratio (an index of BP dipping, defined as the percentage of decrease in BP during the hours of nocturnal rest relative to the mean BP obtained during the hours of daytime activity) and in the so-called morning BP (average BP during the first 2 hours after wake-up time) were compared among groups by repeated-measures ANOVA. The demographic and clinical characteristics in Table S1 were compared between groups by ANOVA (quantitative variables) or nonparametric  $\chi^2$  test. Within-group comparisons of ABPM characteristics (Table) before and after treatment were performed using a paired *t* test.

## Results

### Demographic Characteristics and Analytic Parameters

The demographic characteristics of the 2 treatment-time groups were comparable at baseline, and they remained unchanged after treatment (Table S1). Clinic BP measurements, including pulse pressure, were significantly reduced after treatment ( $P < 0.001$ ) and to a comparable extent in both treatment-time groups (Table). Clinic HR remained unchanged after treatment. The serum values of glucose, creatinine, uric acid, cholesterol, and triglycerides were comparable at baseline between the 2 treatment groups, and they were not significantly changed after treatment.

### Ramipril on Awakening

Figure 1 shows the circadian pattern of SBP (left) and DBP (right) measured by 48-hour ABPM before and after 6 weeks of ramipril ingestion on awakening in the morning. The dark shading along the lower horizontal axis of the graphs represents the average hours of nocturnal sleep across the patients. Results did not vary between the 2 consecutive days of sampling. Therefore, we decided to pool the BP data over an idealized single 24-hour profile to simplify the graphic display of the results. Ramipril treatment resulted in a statistically significant reduction of the 24-hour BP mean

**Table. Demographic and BP Characteristics of Subjects Investigated**

Variable	Before Treatment			After Treatment		
	Awakening	Bedtime	<i>P</i> Between Groups	Awakening	Bedtime	<i>P</i> Between Groups
Patients, n	58	57				
Sex, % men	41.4	49.1	0.404			
Age, y	46.9±12.3	46.5±10.2	0.854			
Clinic SBP, mm Hg*	150.0±15.4	147.6±15.4	0.415	134.9±15.1†	134.4±13.6†	0.843
Clinic DBP, mm Hg*	91.2±6.8	92.0±7.4	0.523	84.3±8.6†	82.7±8.7†	0.338
Clinic pulse pressure, mm Hg*	58.8±10.4	55.6±12.9	0.149	50.6±9.0†	51.7±9.0†	0.543
Clinic HR, bpm*	72.5±12.1	72.3±10.4	0.934	74.0±12.6	71.9±8.7	0.189
Nocturnal rest, h	8.7±0.8	8.7±1.3	0.837	8.7±0.9	8.4±1.0	0.159
Awake SBP mean, mm Hg	134.6±8.7	135.2±6.6	0.684	124.6±13.0†	124.7±7.5†	0.931
Asleep SBP mean, mm Hg	116.1±10.6	119.2±7.4	0.165	111.6±13.5‡	105.7±6.9†	0.005
24-h SBP mean, mm Hg	128.6±8.3	130.4±6.1	0.176	120.2±12.9†	119.2±6.8†	0.653
Awake:asleep SBP ratio, %	13.7±6.2	11.7±6.4	0.180	10.4±5.5†	15.1±5.4†	<0.001
Morning SBP, mm Hg	132.8±9.9	132.8±7.4	0.994	127.0±14.3‡	119.8±8.2†	<0.001
Awake DBP mean, mm Hg	89.7±4.7	90.1±7.1	0.737	82.8±7.4†	81.1±7.4†	0.239
Asleep DBP mean, mm Hg	73.2±7.4	75.1±6.9	0.143	69.1±8.2†	63.6±6.5†	<0.001
24-h DBP mean, mm Hg	84.5±4.6	85.6±6.2	0.262	78.3±7.2†	76.1±6.9†	0.127
Awake:asleep DBP ratio, %	18.3±7.9	16.3±7.6	0.173	16.4±7.9†	21.2±6.7†	<0.001
Morning DBP, mm Hg	85.2±5.6	87.8±6.5	0.032	81.3±9.3‡	77.4±7.7†	0.018
Nondipper, %	32.8	31.6	0.893	41.4	14.0§	0.001
Awake SBP mean	10.0±8.8	10.5±7.1	0.782	7.6±6.5¶	7.7±5.1¶	0.921¶
Asleep SBP mean	4.5±10.6	13.5±6.9	<0.001	3.8±9.3¶	11.2±5.4¶	<0.001¶
24-h SBP mean	8.4±8.8	11.2±5.5	0.059	6.7±6.9¶	8.5±4.2¶	0.093¶
Awake DBP mean	6.9±7.0	9.0±6.0	0.100	7.8±7.8¶	9.9±6.6¶	0.147¶
Asleep DBP mean	4.1±7.9	11.5±5.8	<0.001	5.3±11.8¶	15.1±7.1¶	<0.001¶
24-h DBP mean	6.2±6.8	9.5±4.7	0.004	7.5±8.3¶	11.1±5.5¶	0.008¶

All of the values are shown as mean±SD unless otherwise specified. The awake:asleep ratio, an index of BP dipping, is defined as the percentage of decline in BP during the hours of nocturnal rest relative to the mean BP obtained during the hours of daytime activity and calculated as: [(awake BP mean—asleep BP mean)/awake BP mean] × 100. Morning BP is defined as the average BP during the first 2 hours after wake-up time. Nondipper indicates patients with awake:asleep SBP ratio <10%, using data sampled by ABPM for 48 consecutive hours.

\*Values correspond with the average of 6 clinic BP and HR measurements obtained on each subject in the clinic before commencing 48-hour ABPM.

†*P*<0.001 vs baseline.

‡*P*<0.01 vs baseline.

§*P*<0.05 vs baseline.

||Data show the absolute BP reduction from baseline.

¶Data show the percentage of BP reduction from baseline.

from baseline (decrease of 8.4/6.2 mm Hg in SBP/DBP; *P*<0.001; Table). With morning treatment, 43% of the subjects in this group showed controlled values of ABPM, ie, values below the diagnostic thresholds mentioned above.<sup>7</sup> The effects of treatment were greater on the awake than on the asleep BP mean when ramipril was ingested on awakening (Table). Morning ramipril treatment exerted no effect on the 24-hour HR mean (increase of 0.3 bpm; *P*=0.610).

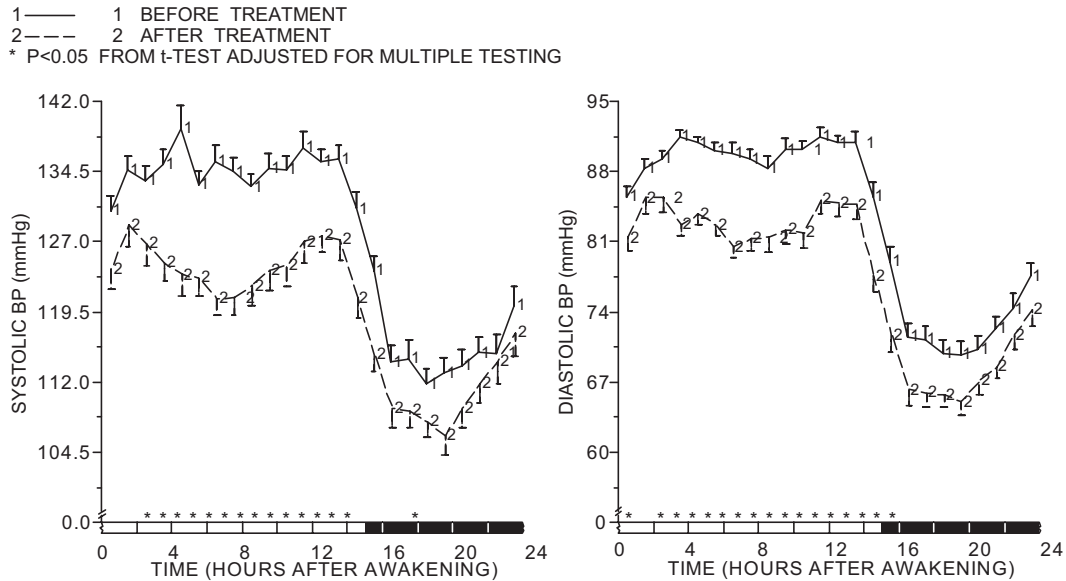
### Ramipril at Bedtime

Figure 2 shows the 24-hour pattern of SBP and DBP before and after ramipril ingested at bedtime. This timed treatment resulted in significant reduction in the 24-hour mean of SBP/DBP from baseline, by 11.2/9.5 mm Hg (*P*<0.001; Table). In keeping with the ABPM criteria mentioned above, 65% of the patients in this group evidenced controlled BP with bedtime treatment. Despite the significant effect on BP,

HR remained unchanged after bedtime treatment (decrease of 1.2 bpm in the 24-hour HR mean; *P*=0.295). BP reduction with treatment at bedtime was statistically significant (*P*<0.001 after correcting for multiple testing) over all of the 24 hourly intervals, as shown by the asterisks above the lower horizontal axis in Figure 2. The effects of treatment were greater on the asleep than on the awake BP mean when ramipril was ingested at bedtime (Table).

### Comparison Between Treatment Groups

There was a lack of statistically significant differences in ambulatory BP at baseline between the 2 treatment-time groups (*P*=0.176 and 0.262 for comparison of 24-hour mean SBP and DBP, respectively; Table). After 6 weeks of timed treatment, the efficacy of ramipril on the awake BP mean was similar for both groups, both in absolute as well as in the percentage of relative changes from baseline (Table). Results,



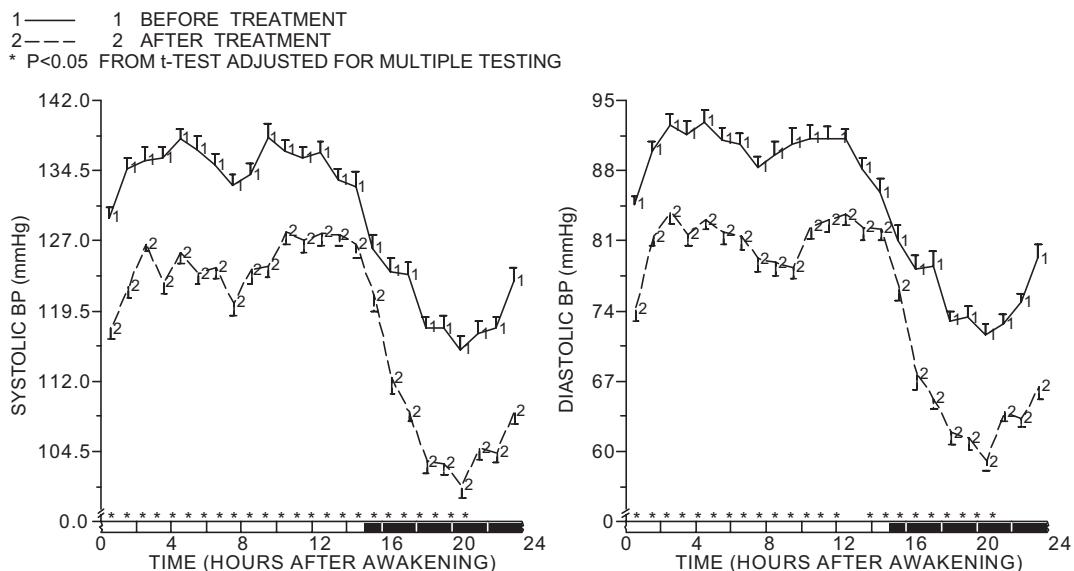
**Figure 1.** Changes in the circadian pattern of SBP (left) and DBP (right) with ramipril (5 mg/d) ingested on awakening in patients with grade 1 or 2 uncomplicated essential hypertension sampled by 48-hour ABPM. Each graph shows the hourly means and SEs of data collected before (continuous line) and after (dashed line) 6 weeks of timed treatment. Dark shading along the lower horizontal axis of the graphs represents the average hours of nocturnal sleep across the patient sample.

however, reveal a greater efficacy with bedtime dosing in regulating asleep BP ( $P < 0.001$  between groups).

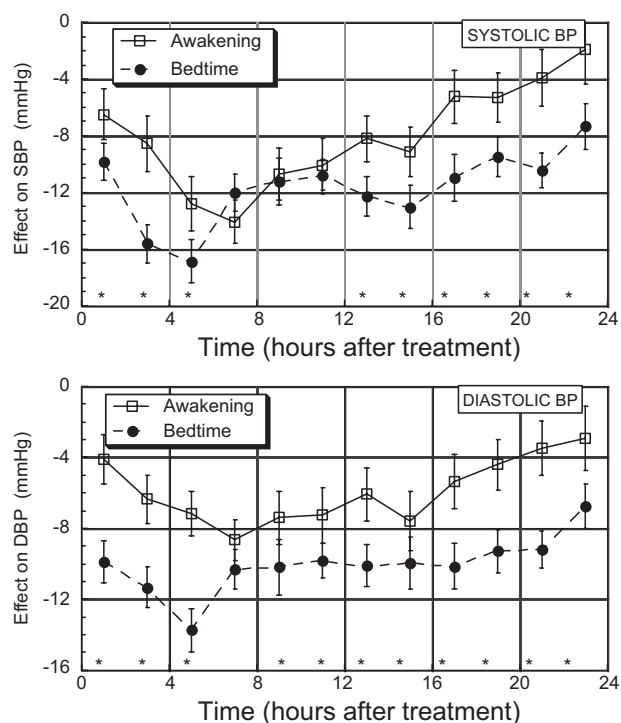
These differing treatment-time effects on nighttime BP are reflected in changes on the sleep-time relative BP decline or awake:asleep BP ratio (Table). There was a significant ( $P < 0.001$ ) increase in this ratio when ramipril was consistently ingested at bedtime and a significant decrease when ramipril was ingested on awakening ( $P < 0.001$  between treatment-time groups; Table). The proportion of patients with a nondipper BP pattern (awake:asleep SBP ratio  $< 10\%$ ) at baseline was increased after ingestion of ramipril on awakening, but the proportion was significantly reduced from

32% to 14% when ramipril was ingested at bedtime ( $P = 0.026$ ; Table).

The effects of ramipril on BP as a function of the time of drug ingestion are illustrated in Figure 3. This figure shows the efficacy of BP lowering in terms of the duration in hours from the last timed dose of ramipril. As shown in Figure 3, ramipril reaches its peak effect sooner when dosed at bedtime, thus showing a significantly greater efficacy during the first 6 hours after treatment. Moreover, efficacy is gradually lost more rapidly when ramipril is ingested on awakening. Thus, the BP reduction is significantly greater during the last 12 hours of the dosing interval with bedtime administration of



**Figure 2.** Changes in the circadian pattern of SBP (left) and DBP (right) with ramipril (5 mg/d) ingested at bedtime in patients with grade 1 or 2 uncomplicated essential hypertension sampled by 48-hour ABPM. Each graph shows the hourly means and SEs of data collected before (continuous line) and after (dashed line) 6 weeks of timed treatment. Dark shading along the lower horizontal axis of the graphs represents the average hours of nocturnal sleep across the patient sample.



**Figure 3.** Changes (in units of mm Hg) from baseline along the 24-hour after treatment in SBP (top) and DBP (bottom) with ramipril (5 mg/d) ingested on awakening or at bedtime in patients with grade 1 or 2 uncomplicated essential hypertension studied by 48-hour ABPM before and after 6 weeks of timed treatment. \* $P < 0.05$  in BP reduction between the 2 groups.

ramipril. These differences in dose-response curve also reflect a markedly different efficacy or morning versus evening ramipril ingestion in controlling morning BP (Table). Thus, the reduction of the average BP during the first 2 hours after wake-up time was more than double when ramipril was administered at bedtime (Table).

Finally, with regard to the safety profile, apart from the 2 patients who withdrew because of secondary effects, 4 additional patients (3 on awakening dosing and 1 on bedtime dosing) reported mild cough. This efficacy trial, however, does not provide the required sample size to properly evaluate potential differences in adverse effects depending of the time of ramipril administration.

### Discussion

Results of this randomized, prospective trial indicate that 5 mg/d of ramipril significantly reduces BP for the entire 24 hours only when the once-daily dose is ingested at bedtime (Figure 3). Morning dosing on awakening, however, has short 16-hour duration of action (Figure 1) and, thus, a significantly reduced efficacy not only during the hours of nocturnal sleep (coincident with the last hours of the dosing interval) but also during the hours immediately after waking up. Ramipril dosing on awakening and at bedtime showed similar efficacy in reducing the awake BP mean (Table); however, the BP-lowering effect was significantly lower on the asleep BP mean after morning as compared with bedtime administration of ramipril. Accordingly, there was a significant decrease in the proportion of nondipper patients only after treatment in

the bedtime-dosing group. This might be clinically relevant, because nondipping has been related to an increase in end-organ injury and cardiovascular events.<sup>9–11</sup> Moreover, independent prospective studies have also concluded that nighttime BP is a better predictor of cardiovascular mortality than the awake or the 24-hour BP means.<sup>9,12,13</sup>

A number of previous publications reviewed elsewhere<sup>3</sup> have documented morning-evening administration-time differences in the pharmacokinetics and/or pharmacodynamics of several different classes of BP-lowering medications. For instance, we have documented previously that the once-daily evening, in comparison with morning, ingestion schedule of the angiotensin receptor blocker valsartan significantly improved the awake:asleep BP ratio,<sup>14</sup> thus markedly modifying the circadian pattern of BP variation. Similar time-dependent effects on ambulatory BP, namely, a more efficient control of nighttime BP without any loss in efficacy during activity with bedtime as compared with morning dosing, were also documented for telmisartan<sup>15</sup> and olmesartan.<sup>16</sup>

Clinical studies also demonstrated different effects of the ACE inhibitors benazepril, enalapril, imidapril, perindopril, quinapril, and trandolapril when dosed in the morning versus the evening.<sup>3,4</sup> In all of the cases, evening administration of these medications resulted in a higher effect on nighttime BP and a significant modification of the circadian BP profile toward more of a dipper pattern.<sup>3</sup> Kuroda et al<sup>17</sup> investigated the effects of the long-acting lipophilic ACE inhibitor trandolapril when ingested just before going to bed or in the morning in 30 hypertensive patients. Bedtime administration of the medication was found to be a safe and effective means of controlling morning BP in hypertensive patients without induction of excessive BP reduction nocturnally.<sup>17</sup> Morgan et al<sup>18</sup> also found, in 18 patients with essential hypertension, that the early morning BP rise was reduced more when perindopril was administered at 9 PM. However, this dose regimen did not reduce BP over 24 hours. In the present study on a much larger number of patients, ramipril also efficiently reduced morning BP and nighttime BP to a greater extent when ingested at bedtime, whereas this timed regimen increased the duration of the therapeutic action of ramipril (Figure 3). Results, however, should not be generalized. Our trial was restricted to white, relatively young, previously untreated patients with essential hypertension, who received the initial 5-mg/d dose of ramipril. Previous results have documented, eg, a significant difference in the response to ramipril according to ethnicity.<sup>19</sup>

With respect to contributing factors to the circadian BP pattern, a prominent circadian variation has been demonstrated for plasma renin activity, ACE, angiotensin II, aldosterone, atrial natriuretic peptide, and catecholamines,<sup>20</sup> all reflecting the marked circadian structure of the renin-angiotensin-aldosterone system. Plasma renin activity has its peak during nighttime sleep and a trough in the early afternoon.<sup>21</sup> Plasma aldosterone presents a circadian pattern with high values at the beginning of daily activity and lower values at the beginning of nocturnal rest. Thus, we hypothesize that the administration time-dependent effects of the ACE inhibitor ramipril on BP demonstrated here might be related to the circadian variation in the renin-angiotensin-aldosterone sys-

tem, with its activation occurring during the nocturnal sleep span and not just a consequence of terminal half-life. This hypothesis might be supported by the increased duration of action and BP control of bedtime as compared with morning dosing of ramipril (Figure 3). Similar conclusions have been proposed earlier regarding administration time-dependent effects on ambulatory BP of valsartan, telmisartan, and olmesartan, angiotensin receptor blockers characterized by a markedly different terminal half-life but all showing greater efficacy and ability to remodel the circadian BP pattern when administered at bedtime.<sup>3</sup>

On the other hand, appreciable ingestion time differences in the pharmacokinetics of BP lowering are well known. They result from circadian rhythms in gastric pH and emptying, gastrointestinal motility, biliary function and circulation, liver enzyme activity, and blood flow to the duodenum, kidney, and other organs, among other factors.<sup>22</sup> Particularly relevant is the circadian pattern in the glomerular filtration rate, with a maximum in the daytime and a minimum at night.<sup>23</sup> Thus, ramipril might be expected to be cleared more slowly overnight, thus potentially prolonging its duration of action (Figure 3).

The potential reduction in cardiovascular risk associated with the normalization of the circadian BP pattern (converting a nondipper to dipper pattern, possible through bedtime administration of an angiotensin receptor blocker or an ACE inhibitor<sup>3</sup>) is still a matter of debate. So far only 1 study has been specifically designed to investigate whether normalizing the circadian BP profile toward more of a dipper pattern by the use of timed therapy reduces cardiovascular risk.<sup>24</sup> Preliminary findings from this trial, where ABPM was repeated periodically during follow-up, indicate that the probability of cardiovascular and cerebrovascular event-free survival is strongly correlated with the awake:asleep BP ratio. Most important, results suggest that increasing this ratio toward more of a dipper pattern decreases cardiovascular risk, whereas decreasing the awake:asleep BP ratio is associated with an increased morbidity and mortality.<sup>24</sup>

In the Heart Outcomes Prevention Evaluation Study,<sup>25</sup> patients in the active treatment group received ramipril at bedtime. Results from a small substudy, in which hypertensive patients were evaluated with 24 hour ABPM, showed a marked BP reduction, particularly during nighttime sleep,<sup>26</sup> thereby reducing the prevalence of nondippers. The authors concluded that the beneficial effects on cardiovascular morbidity and mortality seen with ramipril in the Heart Outcomes Prevention Evaluation Study might relate to the 8% increase in the awake:asleep BP ratio seen after ramipril was administered at bedtime.<sup>26</sup> A recent study with another ACE inhibitor, temocapril, evaluated its time-dependent effect on the mortality of stroke-prone spontaneous hypertensive rats.<sup>27</sup> Temocapril prolonged the survival rate of the animals, with a maximum effect after dosing at the early resting period and a minimal effect after dosing at the early active period. These results are relevant inasmuch as, similar to the results found here for ramipril, evening dosing with temocapril significantly reduces nocturnal BP to a greater extent than diurnal BP and, thus, increases the awake:asleep BP ratio toward a more dipper profile.<sup>28</sup> In light of these collective findings,

evaluation of the potential decrease in cardiovascular risk from the proper modeling of the circadian BP profile by the timed administration of antihypertensive medication (ie, by bedtime dosing of drugs blocking the renin-angiotensin-aldosterone system, eg, ramipril), beyond reduction of BP levels, deserves further prospective investigation.

### Perspectives

The results of this study on subjects with grade 1 or 2 uncomplicated essential hypertension randomly assigned to receive the 5-mg daily dose of ramipril either on awakening or at bedtime demonstrate a normalization of the circadian BP profile toward more of a dipper pattern only when ramipril is administered at bedtime. The change in the dose-response curve, extended duration of therapeutic action, increased proportion of controlled patients, and improved efficacy on nighttime BP with administration of ramipril at bedtime should be taken into account when prescribing this ACE inhibitor for treatment of essential hypertension.

### Sources of Funding

This independent investigator-promoted research was supported in part by unrestricted grants from Dirección General de Investigación, Ministerio de Educación y Ciencia (SAF2006-6254-FEDER); King Pharmaceuticals; Consellería de Presidencia, Relacións Institucionais e Administración Pública, Secretaría Xeral de Investigación e Desenvolvemento, Xunta de Galicia (PGIDIT03-PXIB-32201PR); Consellería de Educación e Ordenación Universitaria, Dirección Xeral de Promoción Científica e Tecnolóxica do Sistema Universitario de Galicia, Xunta de Galicia (to R.C.H.); Consellería de Innovación e Industria, Dirección Xeral de Investigación, Desenvolvemento e Innovación, Xunta de Galicia (INCITE07-PXI-322003ES; INCITE08-E1R-322063ES); and Vicerrectorado de Investigación, University of Vigo.

### Disclosures

None.

### References

- Hermida RC, Ayala DE, Portaluppi F. Circadian variation of blood pressure: the basis for the chronotherapy of hypertension. *Adv Drug Deliv Rev.* 2007;59:904–922.
- Portaluppi F, Smolensky MH. Circadian rhythm and environmental determinants of blood pressure regulation in normal and hypertensive conditions. In: White WB, ed. *Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics*. Totowa, NJ: Humana Press; 2000:79–118.
- Hermida RC, Ayala DE, Calvo C, Portaluppi F, Smolensky MH. Chronotherapy of hypertension: administration-time dependent effects of treatment on the circadian pattern of blood pressure. *Adv Drug Deliv Rev.* 2007;59:923–939.
- Ohmori M, Fujimura A. ACE inhibitors and chronotherapy. *Clin. Exp Hypertens.* 2005;2 and 3:179–185.
- Myburgh DP, Verho M, Botes JH, Erasmus ThP, Luus HG. 24-Hour pressure control with ramipril: comparison of once-daily morning and evening administration. *Curr Ther Res.* 1995;56:1298–1306.
- Lacourcière Y, Neutel JM, Davidai G, Koval S. A multicenter, 14-week study of telmisartan and ramipril in patients with mild-to-moderate hypertension using ambulatory blood pressure monitoring. *Am J Hypertens.* 2006;19:104–112.
- Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker HAJ, Zanchetti A. 2007 guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2007;25:1105–1187.

8. Staessen J, Fagard R, Lijnen P, Thijs L, Vaa Hoof R, Amery A. Ambulatory blood pressure monitoring in clinical trials. *J Hypertens*. 1991; 9(suppl 1):s13–s19.
9. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J, for the Systolic Hypertension in Europe (Syst-Eur) Trial investigators. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA*. 1999;282: 539–546.
10. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S, Imai Y. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama Study. *J Hypertens*. 2002;20:2183–2189.
11. Brotman DJ, Davidson MB, Boumitri M, Vidt DG. Impaired diurnal blood pressure variation and all-cause mortality. *Am J Hypertens*. 2008; 21:92–97.
12. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension*. 2005;46:156–161.
13. Kikuya M, Ohkubo T, Asayama K, Metoki H, Obara T, Saito S, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama Study. *Hypertension*. 2005;45:240–245.
14. Hermida RC, Calvo C, Ayala DE, Domínguez MJ, Coveló M, Fernández JR, Mojón A, López JE. Administration-time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. *Hypertension*. 2003;42: 283–290.
15. Hermida RC, Ayala DE, Fernández JR, Calvo C. Comparison of the efficacy of morning versus evening administration of telmisartan in essential hypertension. *Hypertension*. 2007;50:715–722.
16. Hermida RC, Ayala DE, Chayán L, Mojón A, Fernández JR. Administration-time-dependent effects of olmesartan on the ambulatory blood pressure of essential hypertension patients. *Chronobiol Int*. 2009; 26:61–79.
17. Kuroda T, Kario K, Hoshide S, Hashimoto T, Nomura Y, Saito Y, Mito H, Shimada K. Effects of bedtime vs. morning administration of the long-acting lipophilic angiotensin-converting enzyme inhibitor tran-  
dolapril on morning blood pressure in hypertensive patients. *Hypertens Res*. 2004;27:15–20.
18. Morgan T, Anderson A, Jones E. The effect on 24 h blood pressure control of an angiotensin converting enzyme inhibitor (perindopril) administered in the morning or at night. *J Hypertens*. 1997;15:205–211.
19. Moran A, Simon JA, Shiboski S, Pickering TG, Waters D, Rotter JI, Lyon C, Nickerson D, Yang H, Saad M, Hsueh W, Krauss RM. Differential effects of ramipril on ambulatory blood pressure in African Americans and Caucasians. *Am J Hypertens*. 2007;20:884–891.
20. Angeli A, Gatti G, Masera R. Chronobiology of the hypothalamic-pituitary-adrenal and renin-angiotensin-aldosterone systems. In: Touitou Y, Haus E, eds. *Biologic Rhythms in Clinical and Laboratory Medicine*. Berlin, Germany: Springer-Verlag; 1992:292–314.
21. Bartter FC, Chan JCM, Simpson HW. Chronobiological aspect of plasma renin activity, plasma aldosterone and urinary electrolytes. In: Krieger DT, ed. *Endocrine Rhythms*. New York, NY: Raven; 1979:49–132.
22. Labrecque G, Beauchamp D. Rhythms and pharmacokinetics. In: Redfern P, ed. *Chronotherapeutics*. London, United Kingdom: Pharmaceutical Press; 2003:75–110.
23. Koopman MG, Koomen GC, Krediet RT, de Moor EA, Hoek FJ, Arisz L. Circadian rhythm of glomerular filtration rate in normal individuals. *Clin Sci (Lond)*. 1989;77:105–111.
24. Hermida RC, for the MAPEC Study Investigators. Ambulatory blood pressure monitoring in the prediction of cardiovascular events and effects of chronotherapy: rationale and design of the MAPEC Study. *Chronobiol Int*. 2007;24:749–775.
25. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: the Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145–153.
26. Svensson P, de Faire U, Sleight P, Yusuf S, Östergren J. Comparative effects of ramipril on ambulatory and office blood pressures: a HOPE Substudy. *Hypertension*. 2001;38:e28–e32.
27. Nozawa M, Sugimoto K, Ohmori M, Ando H, Fujimura A. Dosing time-dependent effect of temocapril on the mortality of stroke-prone spontaneously hypertensive rats. *J Pharmacol Exp Ther*. 2006;316: 176–181.
28. Eguchi K, Kario K, Shimada K. Differential effects of a long-acting angiotensin converting enzyme inhibitor (temocapril) and a long-acting calcium antagonist (amlodipine) on ventricular ectopic beats in older hypertensive patients. *Hypertens Res*. 2002;25:329–333.

**Online supplement**

**CHRONOTHERAPY WITH THE ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR  
RAMIPRIL IN ESSENTIAL HYPERTENSION: IMPROVED BLOOD PRESSURE  
CONTROL WITH BEDTIME DOSING**

Ramón C. Hermida, Diana E. Ayala

Bioengineering & Chronobiology Laboratories, University of Vigo, Campus Universitario, Vigo,  
36200 Spain.

SHORT TITLE: Chronotherapy with ramipril.

JOURNAL SUBJECT HEADS: Hypertension, clinical studies, 193.

ADDRESS: Prof. Ramón C. Hermida, Ph.D.  
Director, Bioengineering and Chronobiology Labs.  
E.T.S.I. Telecomunicación  
Campus Universitario  
VIGO (Pontevedra) 36200, SPAIN  
Ph.: 34-986-812148 & 34-986-812146.  
Fax: 34-986-812116.  
E-mail: rhermida@uvigo.es

**Table S1. Demographic and analytical characteristics of subjects investigated. All values are shown as mean±SD.**

Variable	Before treatment			After treatment		
	Awakening	Bedtime	P between groups	Awakening	Bedtime	P between groups
Patients, n	58	57				
Sex, % men	41.4	49.1	0.404			
Age, years	46.9±12.3	46.5±10.2	0.854			
Height, cm	164.3±8.9	163.6±8.5	0.702			
Weight, Kg	76.8±11.0	76.7±8.7	0.909	77.1±11.1	76.3±8.4	0.613
BMI, Kg/m <sup>2</sup>	29.4±4.7	28.8±3.2	0.424	29.5±4.8	28.7±3.3	0.291
Waist, cm	94.2±10.1	92.0±5.7	0.149	93.8±9.9	91.6±6.1	0.159
Glucose, mg/dL	95.2±13.7	95.4±10.9	0.940	97.9±19.8	96.5±11.7	0.660
Creatinine, mg/dL	0.89±0.12	0.90±0.14	0.758	0.90±0.14	0.89±0.16	0.908
Uric acid, mg/dL	5.1±0.9	5.3±0.8	0.210	5.1±0.6	5.4±0.7	0.125
Cholesterol, mg/dL	194.7±37.5	195.4±21.2	0.907	189.5±25.1	197.0±26.9	0.136
Triglycerides, mg/dL	91.2±46.6	91.4±39.9	0.983	91.3±44.7	95.2±47.7	0.657

BMI = body mass index; SBP = systolic BP; DBP = diastolic BP; PP = pulse pressure; HR = heart rate.