Circadian Timing of Aspirin

Time-Dependent Effects of Low-Dose Aspirin on Plasma Renin Activity, Aldosterone, Cortisol, and Catecholamines

Jaapjan D. Snoep, Marcel M.C. Hovens, Sharif M. Pasha, Marijke Frölich, Hanno Pijl, Jouke T. Tamsma, Menno V. Huisman

Abstract—Studies have shown that aspirin may decrease blood pressure when given at bedtime but not when administered on awakening. However, until now, a biologically plausible mechanism of this striking phenomenon was not revealed. We investigated the effect of 100 mg of aspirin administered at bedtime compared with administration on awakening on plasma renin activity and aldosterone levels over 24 hours and excretion of cortisol and catecholamines in 24-hour urine samples. A randomized, placebo-controlled, double-blind, crossover trial was performed in 16 grade 1 hypertensive subjects. During 2 periods of 2 weeks separated by a 4-week washout period, participants used aspirin both at morning and at night, which was blinded with placebo. After both periods, subjects were admitted for 24 hours to measure the aforementioned parameters. Aspirin intake at bedtime compared with on awakening reduced average (24-hour) plasma renin activity by 0.08 μg/L per hour (95% CI: 0.03 to 0.13 μg/L per hour; P=0.003) without affecting aldosterone levels (95% CI: −0.01 to 0.01 nmol/L; P=0.93). Cortisol excretion in 24-hour urine was 52 nmol/24 hours (95% CI: 5 to 99 nmol/24 hours; P=0.05) lower, and dopamine and norepinephrine excretions were 0.25 μmol/24 hours (95% CI: 0.01 to 0.48 μmol/24 hours; P=0.04) and 0.22 μmol/24 hours (95% CI: −0.03 to 0.46 μmol/24 hours; P=0.02) lower in patients treated with bedtime aspirin. In conclusion, aspirin taken at bedtime compared with on awakening significantly diminished 24-hour plasma renin activity and excretion of cortisol, dopamine, and norepinephrine in 24-hour urine. Decreased activity of these pressor systems forms a biologically plausible explanation for the finding that aspirin at night may reduce blood pressure, whereas aspirin at morning does not. (Hypertension. 2009;54:1136-1142.)

Key Words: aspirin ▪ hypertension ▪ circadian rhythm ▪ renin-angiotensin system ▪ catecholamines

One of the most important modifiable risk factors for cardiovascular disease is the presence of arterial hypertension. Therefore, modern guidelines recommend treatment of hypertension with both lifestyle measures and medication to prevent cardiovascular events. A modest reduction of blood pressure (ie, 3 to 5 mm Hg) in the population will already produce a dramatic fall in serious events, such as myocardial infarction and stroke.

Nowadays, low-dose aspirin (acetylsalicylic acid) forms a cornerstone in the secondary prevention of cardiovascular events, particularly because its inhibitory effects on platelet aggregation, which is predominantly based on the irreversible inhibition of cyclooxygenase 1–mediated thromboxane A2 production by platelets. The clinical effectiveness of aspirin on the secondary prevention of cardiovascular events has been well established. Although aspirin is a potent vasoprotective drug, it is generally believed to have no effect on blood pressure. Notably, in studies addressing this association, it was not reported at what time of the day aspirin was ingested by the participants. In contrast, 2 recent randomized, controlled trials by Hermida et al have shown that 100 mg of aspirin strongly decreased blood pressure in subjects with grade 1 essential hypertension when it was administered at bedtime, whereas (if anything) blood pressure might be slightly increased when aspirin was taken on awakening. In the subjects allocated to aspirin at evening, reductions of systolic and diastolic blood pressures of, respectively, 7.2/4.9 and 6.8/4.6 mm Hg (systolic/diastolic blood pressure) were recorded, whereas in the participants using aspirin at morning, a slight elevation of, respectively, 1.5/1.0 and 2.6/1.6 mm Hg was observed.

An important yet unanswered question is by which mechanism(s) aspirin could time-dependently lower blood pressure. Because the main regulators of blood pressure behave according to circadian rhythms, these may be potential targets of time-dependent aspirin therapy. The renin-angiotensin-aldosterone system (RAAS) is more active during early morning hours as a response to the nocturnal fall in blood pressure.

Received April 17, 2009; first decision May 23, 2009; revision accepted September 8, 2009.

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This trial has been registered in the Dutch Trial Register (NTR 1206, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1206).

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Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.109.134825

1136
and renal perfusion pressure. Aspirin given at night may decrease this nocturnal rise of RAAS activity and concomitantly attenuate the nocturnal drop in NO production. Furthermore, among others, hypothalamic-pituitary-adrenal activity and sympathetic autonomous nervous activity, which are well-known regulators of blood pressure, also display circadian variation. Several studies demonstrate that aspirin could influence various regulators of blood pressure. Moreover, other studies suggest that aspirin has time-dependent effects on lipoperoxides, β-adrenergic receptors, and angiotensin II.

To assess the underlying mechanism of the reported time-dependent effect of aspirin on blood pressure, we conducted a randomized, placebo-controlled crossover trial. We investigated the effects of 100 mg of aspirin administered at bedtime compared with 100 mg of aspirin given on awakening on the levels of plasma renin activity and aldosterone over 24 hours, as well as excretion of cortisol and catecholamines in 24-hour urine among subjects with grade 1 hypertension. We hypothesized that intake of aspirin at bedtime compared with intake on awakening attenuates RAAS activity, as well as the other measured determinants of blood pressure, which would provide an explanation of previously found time-dependent effects of aspirin on blood pressure.

Methods

Subjects

Subjects were eligible for participation if they had an untreated grade 1 hypertension, defined as systolic blood pressure between 140 and 159 mm Hg and/or diastolic blood pressure between 90 and 99 mm Hg, and were >18 years old and capable to give informed consent, which are the same inclusion criteria as used by Hermida et al. Subjects were excluded if they had grade 2 or 3 hypertension (blood pressure ≥160/100 mm Hg), evidence of secondary arterial hypertension, any history of cardiovascular disease, diabetes mellitus, or rheumatoid arthritis or known contraindications to the use of aspirin (defined as history of asthma, any bleeding disorder, gastrointestinal tract bleeding, or known allergy to acetylsalicylic acid). Other exclusion criteria were severe renal or hepatic dysfunction, pregnancy, concurrent participation in other research projects or blood donation, and use of blood pressure–lowering medication, nonsteroidal anti-inflammatory drugs, or anticoagulant medication. We also excluded shift workers, because working in shifts may influence circadian rhythms.

Participants were recruited from general practitioners affiliated with the Leiden University Medical Center and from those who participated earlier in trials of our department. All of the subjects gave written informed consent, and the study was approved by the Leiden University Medical Center Medical Ethics Committee and performed in accordance with the Declaration of Helsinki.

Design

The study had a prospective, randomized, placebo-controlled, double-blind, crossover design (Figure 1). After a first screening visit, all of the subjects (n = 16) were assigned to both one 2-week period taking 100 mg of aspirin on awakening and one 2-week period taking 100 mg of aspirin at bedtime, in a randomized order. To guarantee that participants and investigators were blinded for study medication, the trial was placebo controlled. In the period in which subjects were allocated to receive aspirin in the morning, placebos were provided to take at night and vice versa. The first intervention period of 2 weeks was followed by a washout period of 4 weeks. When subjects received aspirin on awakening in the first period, they were treated with aspirin at bedtime in the second intervention period, and subjects received aspirin on awakening when they were first assigned to aspirin at bedtime. Double-blind study medication was prepared and stored at the Department of Clinical Pharmacy of the Leiden University Medical Center. A computer-generated randomization code was also prepared by an independent person at this department.

The participants visited the research site after an overnight fast at the beginning of each 2-week intervention period for instructions, blood sampling, and to receive both aspirin and placebo for that period. After each treatment period, subjects visited the research site after an overnight fast for a 24-hour admission (Table 1). Thus, each subject was admitted twice for 24 hours, both after intervention with aspirin on awakening and aspirin at bedtime. By a structured interview, we asked for compliance, possible adverse events, and changes in medication. To further assess compliance, remaining pills were counted. Noncompliance was defined as remaining pill count of ≥3 or the subject’s acknowledgement of noncompliance. The study
As a secondary end point, 24-hour ambulatory blood pressure monitoring (ABPM) was performed during the 2 admissions of the subjects. The systolic and diastolic blood pressures and heart rate were automatically gauged every 15 minutes from 7:00 AM to 11:00 PM and every 30 minutes during the night. During both admissions, blood pressure was measured in the same arm with a suitable cuff using a validated Mobil-O-Graph ABPM device (IEM GmbH).

**Laboratory Measurements**

At baseline, routine hematologic and chemical variables were determined according to standard procedures. Renin activity in plasma was quantified by transformation of the generated angiotensin I to angiotensin II by converting enzyme and measured by a radioimmunoassay (Diasorin). Aldosterone was measured with a solid-phase radioimmunoassay (DPC). Urinary cortisol samples were purified over a C-18 column and measured with a fluorescence polarization immunoassay on a TDx analyzer (Abbott). Urinary catecholamine (dopamine, norepinephrine, and epinephrine) concentrations were assessed by high-performance liquid chromatography with electron capture detection (ESTA-Coulochem). All of the assays for plasma renin activity, aldosterone, cortisol, and catecholamines were performed blinded after completion of the study.

**Statistical Analysis**

We calculated a required sample size for this crossover trial of 14 patients to have 90% power at the 5% significance level to detect a 10% plasma renin activity reduction by aspirin at bedtime versus aspirin on awakening, assuming a within-patient SD of plasma renin activity of 8%. Because our sample size calculation was on the basis of our primary end point (ie, differential effects of aspirin according to time of intake on underlying mechanisms of blood pressure, primarily plasma renin activity), our study was not powered to find effects on the secondary end point blood pressure.

To describe the characteristics of the subjects included in our study, continuous variables are presented as mean±SD and categorical variables as frequencies (percentages). To describe the outcome characteristics according to time of intake of aspirin, continuous variables are presented as mean±SEM. To estimate the effects of aspirin taken at bedtime versus aspirin taken on awakening on plasma renin activity, aldosterone, cortisol, catecholamines, and blood pressure and their 95% CIs, we used mixed models to deal accurately with the repeated measurements that we had from each participant. More specifically, a unique identification No. for each subject was entered as a random effect in the models, whereas both a variable denoting aspirin use at morning or at night and a variable for each time a measurement of the relevant outcome variable was done were added as fixed effects. In the case of cortisol and catecholamine levels in 24-hour urine, of which we of course had only 1 measurement per intervention period, these models equal simple paired samples t tests. In the latter case, next to the effect estimates from the mixed models, we also provide P values calculated with the nonparametric Wilcoxon signed-rank test, because these comparisons are based on relatively few numbers, and the differences in those parameters tend to be skewed.

All of the statistical analyses were performed using SPSS version 17.0 (SPSS Inc). All of the analyses were 2-sided, with a level of significance of α=0.05.

**Results**

We included a total of 16 subjects in our crossover trial. Subjects were included between March 2007 and January 2008. All of the subjects were compliant to study medication, and no adverse events occurred. Subject characteristics are summarized in Table 2. Thirty-one percent of the participants were women, and the mean age of all of the subjects was 58 years (range: 47 to 68 years). Baseline office systolic and diastolic blood pressure levels were 147±12 and
86±6 mm Hg, respectively. None of the participants used any relevant comedication, especially nonsteroidal anti-inflammatory drugs or antihypertensive drugs. The total volumes of urine collected during the 24-hour admissions were 2191±591 and 2286±612 mL for intervention with aspirin on awakening and at bedtime, respectively, indicating complete urine collection after both interventions (P=0.49 for difference).

Effects on Mechanisms Underlying Blood Pressure
The effects of 100 mg of aspirin intake at bedtime versus 100 mg of aspirin intake on awakening are summarized in Table 3 and Figures 2 and 3. Aspirin intake at bedtime compared with on awakening reduced the average plasma renin activity over 24 hours by 0.08 μg/L per hour (95% CI: 0.03 to 0.13 μg/L per hour; P=0.003) versus aspirin on awakening, which is a 14% (95% CI: 5% to 22%) reduction (Figure 1). The reduction was observed during the whole 24 hours of observation. At 8:15 AM, after 30 minutes of ambulation after awakening, the reduction of plasma renin activity by aspirin at night compared with aspirin at morning was 0.24 μg/L per hour (95% CI: 0.00 to 0.48 μg/L per hour; P=0.05), which is a 31% (95% CI: 0% to 60%) reduction.

Overall, time of intake of aspirin did not influence plasma levels of aldosterone (mean difference: 0.00 nmol/L [95% CI: −0.01 to 0.01 nmol/L]; P=0.93). Observing the patterns over 24 hours (Figure 3), aldosterone levels seem to be lower at daytime in favor of aspirin intake at bedtime, whereas during the night (particularly early morning), the levels seem to have a reverse pattern.

Aspirin taken at bedtime compared with on awakening also lowered the excretion of cortisol in 24-hour urine. The absolute reduction was 52 mmol/24 hours (95% CI: 5 to 99 mmol/24 hours; P=0.05), whereas the relative reduction was 16% (95% CI: 5% to 30%). Concerning catecholamines measured in 24-hour urine samples, aspirin at night was also favorable compared with intake at morning. Dopamine levels were lowered by 0.25 μmol/24 hours (95% CI: 0.01 to 0.48 μmol/24 hours; P=0.04), which is a 14% (range: 1% to 28%) reduction. The effect on norepinephrine was an absolute reduction of 0.22 μmol/24 hours (95% CI: −0.03 to 0.46 μmol/24 hours; P=0.02), whereas the relative reduction was as high as 40% (95% CI: −1% to 88%). The circadian timing of aspirin had no effect on excretion of epinephrine in 24-hour urine, because the reduction by aspirin taken at night was

Table 2. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Included Subjects (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.4±6.8</td>
</tr>
<tr>
<td>Female sex</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Systolic tension, mm Hg</td>
<td>147±12</td>
</tr>
<tr>
<td>Diastolic tension, mm Hg</td>
<td>86±6</td>
</tr>
<tr>
<td>Heart rate, n/min</td>
<td>64±7</td>
</tr>
<tr>
<td>Smoking</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.6±3.1</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.4±1.0</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>5.2±0.4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.8±0.6</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.0±0.7</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.8±0.7</td>
</tr>
</tbody>
</table>

Data are n (%) or mean±SD. BMI indicates body mass index, calculated as weight (in kilograms) divided by square height (in meters); HbA₁c, glycylated hemoglobin A; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3. Effects of Circadian Timing of Aspirin Intake on Mechanisms Underlying Blood Pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aspirin on Awakening (n=16)</th>
<th>Aspirin at Bedtime (n=16)</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity, μg/L per hour*</td>
<td>0.58±0.11</td>
<td>0.50±0.08</td>
<td>0.08 (0.03 to 0.13)</td>
<td>0.003</td>
</tr>
<tr>
<td>Aldosterone, nmol/L*</td>
<td>0.12±0.01</td>
<td>0.12±0.02</td>
<td>0.00 (−0.01 to 0.01)</td>
<td>0.93</td>
</tr>
<tr>
<td>Cortisol, nmol/24 h</td>
<td>328±34</td>
<td>276±33</td>
<td>52 (5 to 99)</td>
<td>0.05</td>
</tr>
<tr>
<td>Dopamine, μmol/24 h</td>
<td>1.74±0.10</td>
<td>1.49±0.12</td>
<td>0.25 (0.01 to 0.48)</td>
<td>0.04</td>
</tr>
<tr>
<td>Norepinephrine, μmol/24 h</td>
<td>0.52±0.11</td>
<td>0.31±0.04</td>
<td>0.22 (−0.03 to 0.46)</td>
<td>0.02</td>
</tr>
<tr>
<td>Epinephrine, μmol/24 h</td>
<td>0.02±0.008</td>
<td>0.02±0.006</td>
<td>0.00 (−0.01 to 0.01)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Data are mean±SEM and mean difference (95% CI). Positive differences denote an effect in favor of aspirin at bedtime, whereas a negative difference indicates an effect in favor of aspirin on awakening.

*Levels and differences of plasma renin activity and aldosterone are average values of all of the measurements over 24 hours.
Effects on Blood Pressure

As a secondary end point, we assessed the potential time-dependent effect of aspirin on blood pressure itself. The mean systolic and diastolic blood pressures measured by 24-hour ABPM, respectively, were 133.4±3.1 and 85.2±2.5 mm Hg after treatment with aspirin in the morning, whereas those values were 133.8±3.1 and 85.8±2.5 mm Hg after the intervention period with aspirin in the evening. This results in differences of, respectively, −0.5 mm Hg (95% CI: −1.4 to 0.4 mm Hg) and −0.7 mm Hg (95% CI: −1.4 to 0.6 mm Hg), thus, timing of aspirin did not influence the average blood pressure over 24 hours measured by ABPM. Interestingly, in analogy to the 24-hour patterns of aldosterone, there seems to be a small but significant difference in systolic blood pressure during the daytime in favor of aspirin at bedtime (1.3 mm Hg [95% CI: 0.1 to 2.5 mm Hg]; P=0.03), whereas the pattern seems to be reversed during the night (−2.4 mm Hg [95% CI: −3.7 to 1.2 mm Hg]; P<0.001).

Discussion

Previous studies showed that treatment with aspirin may decrease blood pressure when given at bedtime, whereas administration of aspirin in the morning slightly increased blood pressure.8,9 However, until now, a biologically plausible explanation of this striking phenomenon was not revealed in a clinical study. We specifically conducted a randomized, double-blind crossover trial among grade 1 hypertensive subjects to study the underlying mechanism of the potential blood pressure–lowering effect of aspirin at evening but not in the morning. Our main finding is that aspirin administered at night compared with intake in the morning statistically significantly diminished plasma renin activity over 24 hours, as well as excretion of cortisol, dopamine, and norepinephrine in 24-hour urine.

Time-Dependent Effects on Regulators of Blood Pressure

The results of our study corroborate past experiments that indicated that aspirin might influence various regulators of blood pressure.18–23 However, those studies did not address potentially differential effects according to the timing of aspirin intake. A few older reports already suggested that aspirin might have some time-dependent effects.24,25,27 For the first time, we demonstrated statistically significant differential effects according to time of intake of aspirin on plasma renin activity, cortisol, and catecholamines in our clinical study.

Important questions to address are why and how aspirin intake at night confers those effects on underlying mechanisms of blood pressure compared with ingestion in the morning. In the late evening there is probably a window of opportunity to influence those systems by aspirin, in contrast with the early morning. Because RAAS activity and levels of cortisol and catecholamines all display a circadian pattern with an increase in the early morning hours, an explanation may be that administration of aspirin in the morning is simply too late to influence the nocturnal rise in activity of those systems, whereas intake at bedtime might be the right timing to result in a longer-lasting blood pressure–lowering effect.11,12,17 Indeed, we showed that the activity of renin in plasma rises in the early morning hours, whereas it decreases spontaneously (independent of intervention) after the morning peak (Figure 2). According to this potential explanation, the time-dependent effect of aspirin would be particularly based on the time-dependent bioavailability of its substrate. This is corroborated by an animal study in which oral intake of aspirin prevented the increase in blood pressure that occurred in animals that were not treated by aspirin, induced by chronic angiotensin II infusion, whereas intake of aspirin alone, without angiotensin II, did not reduce blood pressure.22 In other studies, aspirin also influenced the response (eg, hypothalamic-pituitary-adrenal activity or hydrogen peroxide–mediated toxicity) on stimulation with various vasoactive substances.18–20,28 Future studies are warranted to further elucidate these and other questions, for example, which of the blood pressure regulating systems is primarily affected by aspirin.

We did not observe an effect on average plasma aldosterone levels over 24 hours. The most likely explanation is that potential RAAS-mediated effects of time of intake of aspirin on blood pressure do not act via aldosterone as an effector hormone, but, for example, via angiotensin II. Previous literature provides no evidence supporting effects of aspirin on aldosterone, whereas there are several reports that reported effects of aspirin on angiotensin II and downstream effects.22,25 Unfortunately, we were not able to measure levels of angiotensin II levels to support or reject the latter hypothesis. Therefore, the present results call for future studies to elucidate the time-dependent effects of aspirin on RAAS in more detail.

Time-Dependent Effects on Blood Pressure

We did not observe a decrease in 24-hour blood pressure by administration of aspirin at bedtime compared with aspirin
given on awakening. There are several explanations for this finding. Our study was not designed and powered to find effects of timing of aspirin on blood pressure but to study effects on mechanisms underlying blood pressure. In addition, the intervention period in our study was only 2 weeks, whereas in earlier studies the participants received aspirin for a period of 3 months.\(^8\)\(^9\) We hypothesize that treatment with aspirin at night for 2 weeks is long enough to obtain differences in blood pressure-regulating systems but not to translate those effects into blood pressure lowering. Interestingly, our results regarding both aldosterone and systolic blood pressure suggest an effect in favor of aspirin at bedtime compared to on awakening during daytime, whereas these patterns were not observed or even tended to reverse during the night.

Study Limitations and Strength

There are limitations to our study. In our crossover study we compared aspirin given at bedtime with aspirin given on awakening, which was blinded by the use of placebos. We did not compare either aspirin in the morning or aspirin in the evening with only placebo. This would have required another crossover and a third intervention period, which would have been more aggravating for the participants. However, we do not consider this as a real limitation, because even if aspirin in the morning also had some effects on our end points (which is not likely), this would only have underestimated our findings to some extent. Furthermore, we were not able to measure angiotensin II as an effector hormone of the RAAS or effects on NO metabolism, which might also provide an explanation for the observed time-dependent effects of aspirin on blood pressure.\(^10\)\(^11\)\(^12\)\(^13\) The major strength of our study is that we used a randomized, double-blind crossover design. Using this design, the same patients were randomly exposed to both interventions in different treatment periods and, therefore, served as their own controls. This unique characteristic of crossover studies maximizes the power to detect an effect and virtually excludes the risk of confounding.

Perspectives

Our study demonstrates that aspirin taken at bedtime compared with aspirin intake on awakening results in a statistically significantly diminished activity of different biological regulators of blood pressure: plasma renin activity over 24 hours and excretion of cortisol, dopamine, and norepinephrine in 24-hour urine were found to be decreased. Reduced activity of these pressor systems forms a biologically plausible explanation for the finding that aspirin at night may reduce blood pressure, whereas aspirin in the morning does not. Before this strategy may be implemented in clinical practice, future studies are warranted to assess whether the blood pressure-lowering effects of aspirin taken at bedtime are sustained in patients who have a clinical indication to be treated with aspirin, that is, patients at high risk of (recurrent) cardiovascular events. This may be challenging, because these patients are likely treated with a variety of antihypertensive drugs, which may dilute or interact with the time-dependent effects of aspirin on blood pressure. Another unanswered but important research question is whether effects of aspirin on platelet aggregation vary according to time of intake. Ultimately, clinical end point studies are needed to answer the final question of whether aspirin given at bedtime will lead to incremental cardiovascular protection beyond treatment on awakening.

Acknowledgments

We thank Marjolijn J. van Glabbeek, MD, for her effort to include study participants, as well as Bep Ladan and Ieneke van der Steen for their support as research nurses.

Sources of Funding

The study has not been funded by any external funding source and has been sponsored by the Leiden University Medical Center.

Disclosures

None.

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Hypertension. 2009;54:1136-1142; originally published online October 5, 2009; doi: 10.1161/HYPERTENSIONAHA.109.134825

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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