Blood pressure varies throughout the day, being highest on awakening in the morning and lowest during sleep. However, the sleep blood pressure predicts cardiovascular and cerebrovascular ischemic events better than the awake blood pressure, which predicts hemorrhagic strokes. Thus, the level of blood pressure interacts with the hormonal environment to determine the outcome. Similar observations have been made in rats in which the blood pressure during sleep is the principal determinant of cardiac enlargement. A conclusion is that control of sleep blood pressure may be more important than control of awake blood pressure, although ideally blood pressure should be controlled throughout 24 hours. Relatively little attention has been paid to the time at which drugs should be administered, and, in general, the ideal is thought to be that they can be taken once a day and usually in the morning, because this is believed to improve compliance. This policy may lead to major undertitration of drugs, particularly those that have a short half-life or duration of action. Thus, the response to enalapril 5, 10, 20 or 40 mg is similar 3 to 4 hours after administration, but the 2 lower doses have little effect 24 hours later. The policy of taking the medication in the morning, particularly if the patient is seen 2 to 3 hours later, leads to a failure to control blood pressure during sleep and during the awakening hours, which probably compose the most critical period. A similar problem applies to most of the angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, although it varies according to the duration of effect (half-life) of the individual agents. Thus, the usual pattern of management may lead to serious undertitration.

The daily variation in blood pressure relates in part to the changing pattern of sympathetic activity and renin angiotensin levels. When awake, sympathetic activity is relatively high, and the baroreceptors control blood pressure, keeping it relatively constant despite widely varying inputs. During sleep, cardiovascular sympathetic activity is reduced and renin secretion increases and is probably the controller of blood pressure. If drugs are used that act relatively independent (diuretics and calcium blockers) of these systems, the response would be expected to be similar during the asleep and awake hours, and this appeared to be the situation in elderly male hypertensive patients. However, the response to drugs that work on these systems may vary according to whether a person is awake or asleep, and this appeared to be the situation, with little response to β-blockers during the sleep hours and increased responsiveness to ACE inhibitors during the sleep period. To ensure that we control blood pressure throughout the 24 hours, we need to choose an appropriate class of drug and use it in a dose that provides appropriate plasma levels to reduce blood pressure throughout the 24-hour interval. We also need to be aware that the handling of drugs (pharmacokinetics) may alter according to the time that the drug was given.

The article in this issue by Hermida and Ayala addresses the important issue of whether it matters at what time of the day medication is taken. They have compared the effect of administration of ramipril (5 mg) given in the morning on awakening or at night before going to bed. They have accessed the response by ambulatory blood pressure monitoring, carefully dividing the periods into awake and asleep times. The patients had not been treated previously for blood pressure. The results unequivocally demonstrate that administration at night improves blood pressure control, as assessed by ambulatory blood pressure monitoring. When given at night there was a significant reduction in blood pressure at all times of the day, whereas when given in the morning, the fall in blood pressure overall was not significant in the last 8 hours. This covers the sleep and awakening periods, during which time blood pressure control is most important. The fall in sleep blood pressure with nighttime administration was 9.0/7.4 mm Hg greater than with morning administration, whereas the fall in awake blood pressure was similar. The fall in sleep systolic blood pressure of 13.5/11.5 mm Hg with nighttime administration was greater than the fall at any other time period, despite the starting blood pressure being lower. If the response of blood pressure to ACE inhibition was similar throughout the 24 hours, a likely explanation of the results would be that the pharmacokinetics of the drug differed and that the drug, when administered at night, was excreted more slowly, leading to a more prolonged effect. However, the greater fall in the 6 hours after the dose indicated that, in addition, the response to ACE inhibitors is greater during the sleep hours. These results differ from previous results reported with perindopril in which the dose given at night did not control blood pressure during the last part of the dosing interval, whereas the morning dose did. It is difficult, however, to compare these studies, because the drugs have different pharmacokinetics, and the doses are not necessarily compatible. However, both studies suggested that sleep blood pressure responds better than daytime blood pressure to ACE inhibition, and it is possible that this response may be at a lower plasma level of the drug. This appeared to be supported by a study with trandolapril in which, during 48-hour monitoring after the last dose, the...
blood pressure response appeared to disappear 30 to 40 hours after administration but reappeared in the last 8 hours when the person was asleep. The results of the present study by Hermida and Ayala5 would have been more definitive if plasma levels of ramipril or the extent of ACE inhibition had been measured at the various time periods.

An analysis of the Heart Outcomes Prevention Evaluation,8 Perindopril Protection Against Recurrent Stroke,8 and European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease10 studies indicates that nighttime administration may have important outcome advantages. In the Heart Outcomes Prevention Evaluation Study, ramipril (10 mg) was given at night and reduced most adverse outcomes by 25%. In the perindopril-only arm of the Perindopril Protection Against Recurrent Stroke Study, perindopril (4 mg) was given in the morning and had no effect on the same outcomes. In the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease Study, perindopril (8 mg) was given in the morning and had a similar reduction in outcomes as in the Heart Outcomes Prevention Evaluation Study. Perindopril (4 mg) may not have adequately controlled blood pressure when asleep, although it was probably well controlled in the other 2 studies.

If an ACE inhibitor is used in a dose that is fully effective throughout 24 hours, the time of administration is probably of little importance. However, if the duration of effect is uncertain, it would seem that nighttime administration is to be preferred. This is particularly the case for ACE inhibitors and probably angiotensin receptor blockers that have a relatively short half-life. If the medication is taken at night and the blood pressure is measured in the morning or afternoon, the drug is more likely to be titrated to a dose that works for 24 hours. If the drug is given in the morning and blood pressure measured later in the day, the drug will probably not be titrated to levels that provide 24-hour blood pressure control. Thus, control will be inadequate at the time (sleep and awakening) when control is most critical. The data can probably also be applied to angiotensin receptor blockers but not to other drug classes.

Disclosures
None.

References
4. Morgan TO, Anderson A. Different drug classes have variable effects on blood pressure depending on the time of day. Am J Hypertens. 2003;16:46–50.