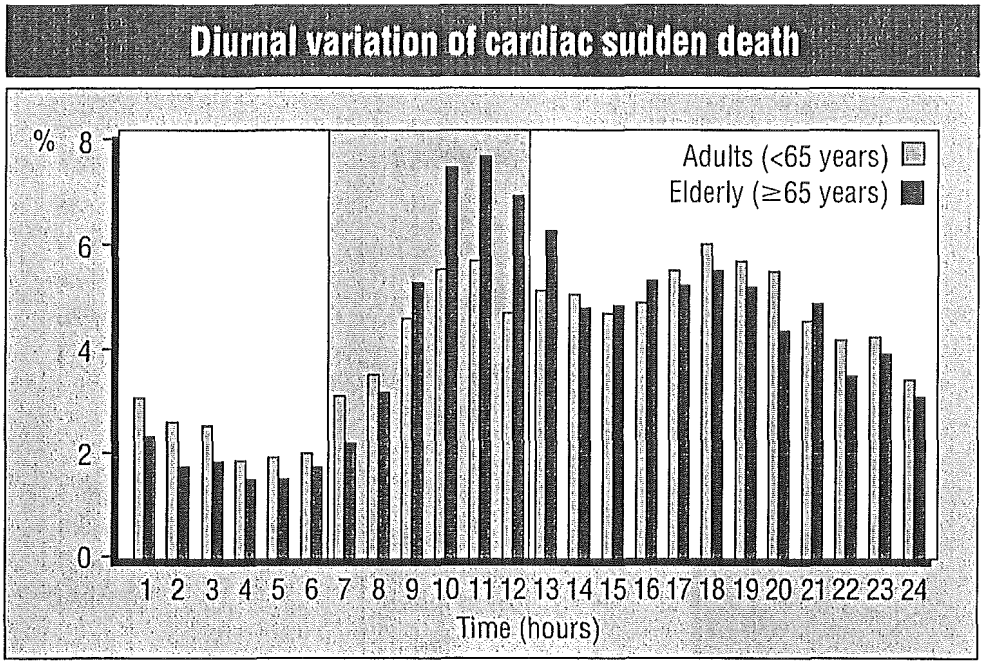

Figure 2.13. *Population-based Berlin Medical System data (24,061 consecutive cases). Reproduced with permission from* Eur Heart J *2000; **21**:315–320.*

Thus, the management of morning BP surge and morning hypertension should be more strictly monitored in high-risk hypertensive patients who are likely to have impaired autoregulation, such as patients with diabetes, elderly patients and patients with LVH, microalbuminuria and other target organ damage. In these high-risk patients, morning BP levels should be monitored by home BP monitoring or by ABPM, even if they are normotensive at clinic BP.

3

Mechanism of morning cardiovascular risk

The mechanism by which the morning BP surge might increase hypertensive target organ damage and trigger cardiovascular events in the morning hours is unclear. In the recent JMS ABPM study (Wave 1), the incidence of morning-onset stroke was significantly higher in the morning surge group than in the nonsurge group. Of the 44 stroke events, 30 were ischaemic, six were haemorrhagic and eight were unknown, however, there was no significant difference in the incidence of haemorrhagic strokes [44]. Thus, the increase in BP during the morning BP surge may not fully explain the increased occurrence of stroke in the morning. Other risk factors activated simultaneously with the morning BP surge may contribute to trigger cardiovascular events (*see* Figure 3.1) [43].

Sympathetic activation

Increased sympathetic activity, particularly the alpha-adrenergic component [56], increases vascular tone in the resistance arteries and may contribute to the morning BP surge. In addition, coronary spasms are more likely to occur in the morning. An increase in plasma cortisol levels could enhance coronary artery sensitivity to the vasoconstrictor effects of catecholamines. In particular, morning BP surge associated with alpha-adrenergic activity is closely associated with multiple silent cerebral infarcts in older hypertensive patients [57].

Endothelial dysfunction

Even in healthy patients, flow-mediated dilatation of the brachial artery was diminished in the early morning when compared with other periods (later in the morning and in the evening), while nonflow-mediated dilatation was comparable in the morning and in other periods (*see* Figure 3.2) [58]. The degree of morning endothelial cell dysfunction found in healthy subjects was similar to that found in high-risk patients with cardiovascular risk factors, such as diabetes and hyperlipidaemia.

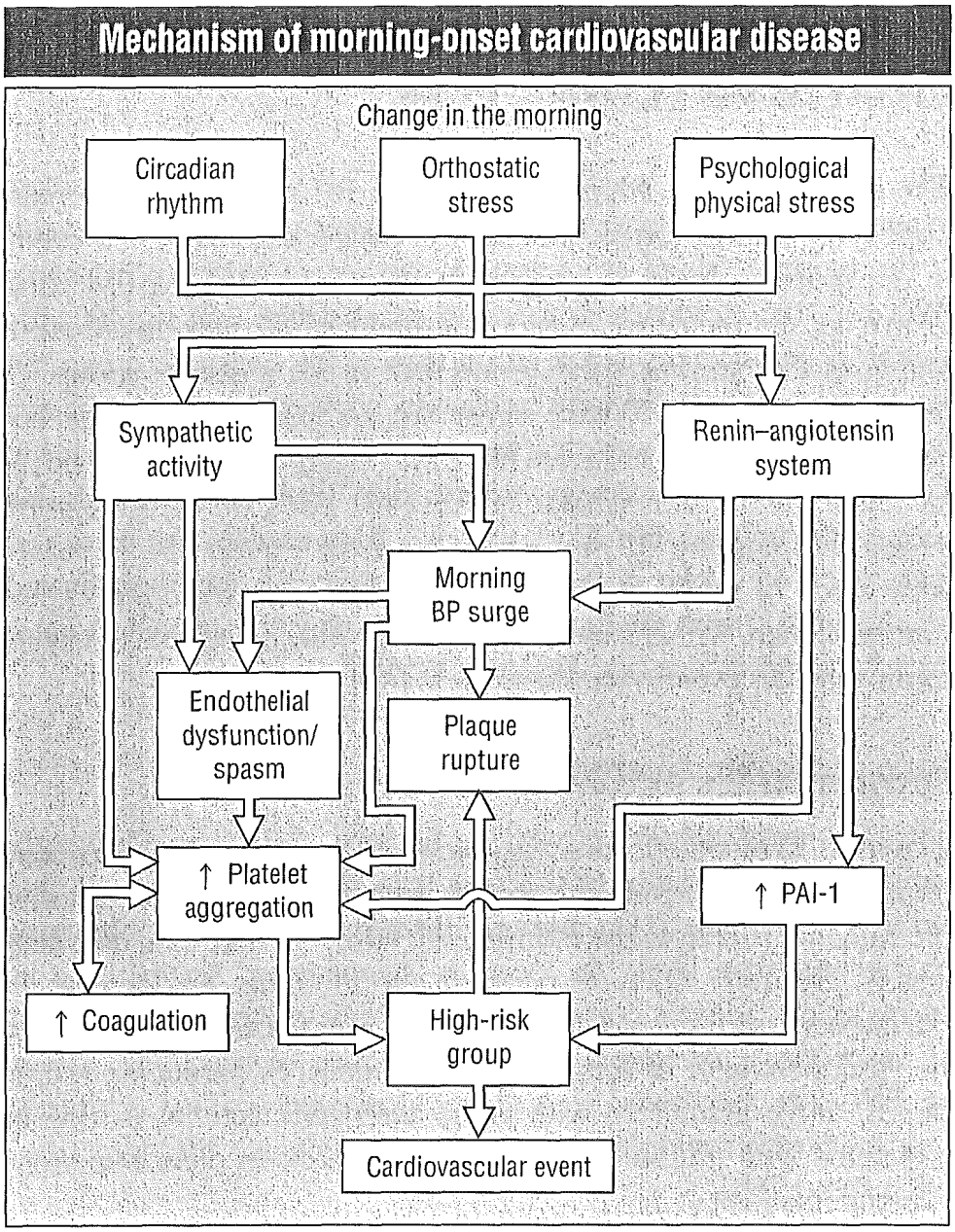

Figure 3.1. *PAI-1, plasminogen activator inhibitor-1. Reproduced with permission from* J Cardiovasc Pharmacol *2003;* ***42*** *(Suppl):S87–S91.*

Platelet hyperactivity

Other contributory changes include increased platelet aggregability and increased haematocrit and levels of fibrinogen, which both lead to increased blood viscosity. The potentiation of these factors is partly triggered by getting out of bed in the morning [59]. One mechanism by which the morning BP surge may trigger vascular

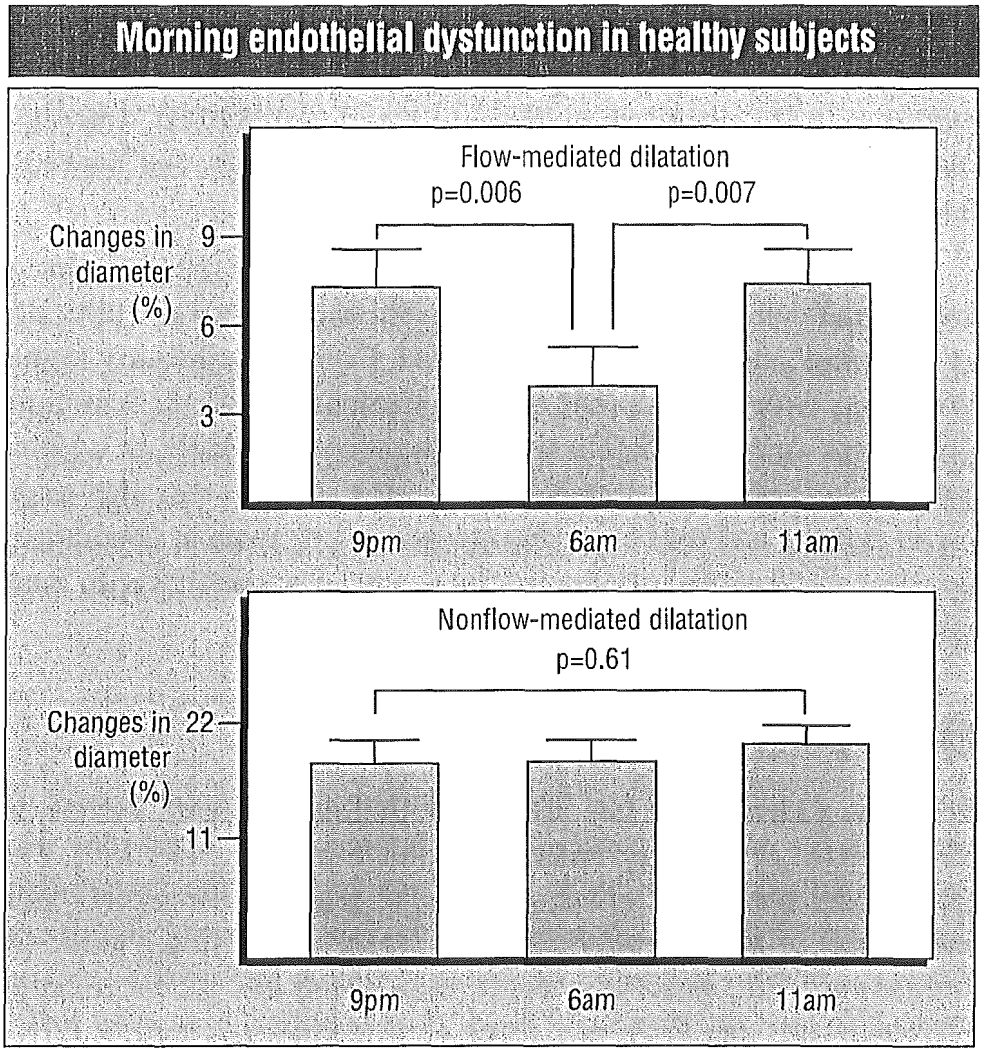

Figure 3.2. *Healthy subjects (n=30, mean age=41.6 years). Reproduced with permission from* Circulation *2004;* ***109****:2507–2510.*

spasm is increased shear stress on the vascular wall. In addition, platelets may be activated by high shear stress occurring at stenotic areas of atherosclerotic arteries, therefore, morning BP surge could trigger increased platelet aggregation in the morning [60].

Haemostatic abnormality

As well as increased thrombophilic tendencies in the early morning, plasminogen activator inhibitor-1 (PAI-1), which inhibits tissue-type plasminogen activator leading to impaired fibrinolysis, also shows a morning increase [61]. PAI-1 production levels are

partly regulated by a peripheral clock gene [62] and partly by components of the RAAS system (shown by the infusion of angiotensin II causing an increase in PAI-1 levels [63]). Together, the potentiation of these cardiovascular risk factors, can lead to a morning thrombogenic tendency.

Morning plasma levels of von Willebrand factor (an indicator of endothelial cell stimulation), prothrombin fragments 1+2 (indicator of thrombin generation *in vivo*) and PAI-1 were significantly higher in patients with diabetes [64] and in hypertensive patients with multiple silent cerebral infarcts when compared with patients without such infarcts [65]. These factors may also advance vascular target organ damage and lead to cardiovascular events. Even in nondiabetic hypertensive patients, plasma insulin levels are associated with these haemostatic abnormalities in insulin resistance [65].

Clock gene

Recently, a clock gene has been identified in peripheral tissues, as well as in the central suprachiasmatic nucleus of the brain [66]. The central and peripheral clock genes may regulate the metabolism and effects of the neurohumoral risk factors exhibiting significant diurnal variation, although the extent to which this occurs remains unclear. In fact, the peripheral clock gene is known to modify PAI-1 production and the RAAS system, partly contributing to diurnal variation of these factors [62,67].

Stress and poor sleep quality

In high-risk patients with vascular damage caused by chronic risk factors, such as diabetes, hypertension, hyperlipidaemia and smoking, the morning potentiation of the risk factors exhibiting diurnal variation, might additively and synergistically trigger cardiovascular events. As well as morning potentiation, these risk factors are also known to change due to stress. It has previously been found that haemostatic risk factors and BP were also potentiated by acute catastrophic stress following an earthquake [68–70]. Stressful events and poor sleep quality would also modify these morning risk factors.

4

Morning hypertension as a predictor of cardiovascular risk

Clinical implications of morning blood pressure level

The self-measured morning home BP level has been shown to be the best predictor for cardiovascular death in a community-based population [71]. In the JMS ABPM study (Wave 1), morning BP levels (measured as an average of BP during the two hours after rising) were the best predictors for stroke events in older hypertensive patients [43]. Controlling for clinic BP level and also for 24-hour BP level, morning BP levels remain a significant predictor of stroke events. Thus, the morning BP level measured by home BP monitoring or ABPM may have specific clinical implications for assessing hypertensive target organ damage and cardiovascular prognosis.

In hypertensive patients treated with antihypertensive medication, the monitoring of morning BP level is an important indication of the overall BP control status. Recent developments in clinical practice for hypertension mean that many antihypertensive agents are available for once daily dosing in the morning. However, frequently, the BP lowering effect of the drug does not persist for a 24-hour period. Even among well-controlled hypertensive patients in clinics, many will show increased uncontrolled morning hypertension. Recently, the Jichi Morning-Hypertension Research (J-MORE) pilot study [72,73] investigated a total of 1027 consecutive hypertensive patients taking the same antihypertensive medication for at least three months. Patients were recruited from 43 doctors in 32 different clinics in Japan and an analysis was conducted in 990 samples (age: 66.2±10.3 years [mean±SD]) after the exclusion of 37 night-shift workers. Home BP monitoring was conducted twice in the morning, just before taking antihypertensive medication, and in the evening, just before going to bed, for three consecutive days using automatic devices (*see* Table 4.1).

In the total number of treated hypertensive patients, the prevalence of well-controlled hypertension (<140 mmHg SBP and <90 mmHg diastolic BP by clinic measurements) was 41.5%. As there is

Jichi Morning-Hypertension Research Pilot Study patient profile
Percentage of patients with concomitant cardiovascular diseases
• Stroke – 7.3% • Coronary artery disease – 11.8% • Renal failure – 4.9% • Smoker – 12.3% • Hyperlipidaemia – 40.7% • Diabetes – 13.3%
Percentage of patients taking antihypertensive medications
• Calcium antagonists – 34.0% long-acting, 7.5% short- or intermediate-acting • ACE inhibitors – 14.4% long-acting, 0.8% short- or intermediate-acting • ARBs – 17.9% • Diuretics – 6.9% • Alpha-adrenergic blockers – 9.8% • Beta-adrenergic blockers – 5.8% • Others – 2.9%.

Table 4.1. *ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers.*

no consensus on home BP levels for the definition of hypertension, cut-off values proposed by the American Hypertension Society of 135/85 mmHg for morning BP were used [4]. In well-controlled hypertensive patients, more than half (60.6%) exhibited high morning BP levels (≥135 mmHg SBP or ≥85 mmHg diastolic BP). This subgroup was named 'masked morning hypertension'. Figure 4.1 shows the control status of SBP, this morning hypertension is currently the blind spot of clinical practice in hypertension.

The Analysis of the Control of Blood Pressure using Ambulatory Blood Pressure Monitoring (ACAMPA) study in Spain [74], a multicentre, open, prospective, observational study using

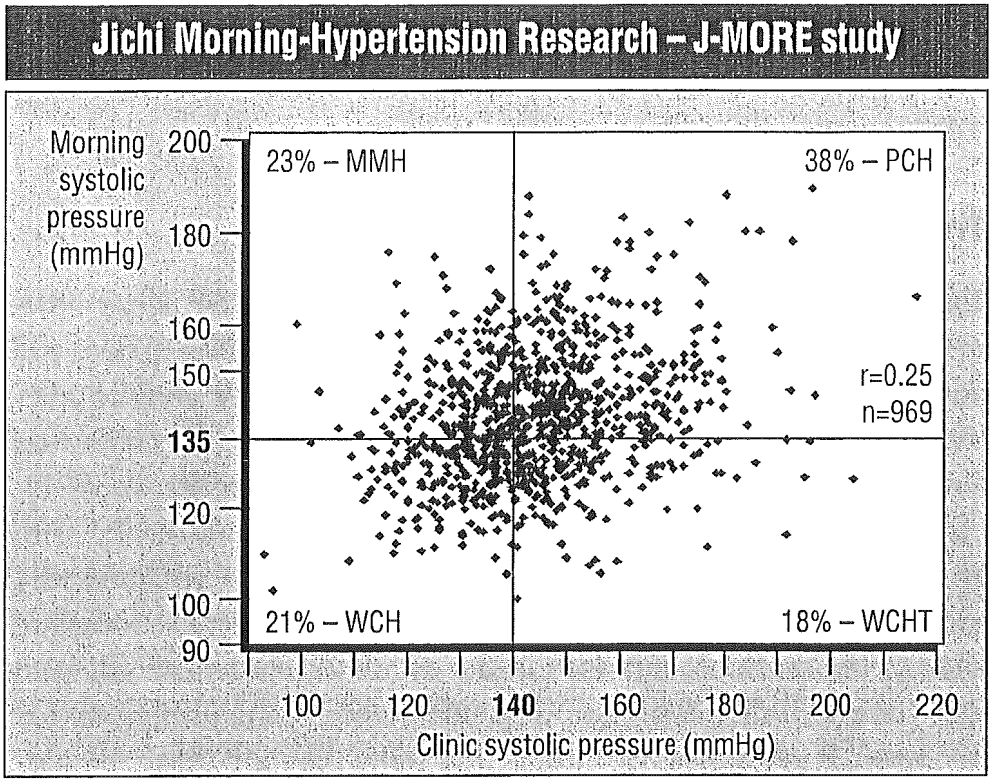

Figure 4.1. *Medicated hypertensive patients (n=969; mean age 66.5 years, men 42%) were recruited from 45 doctors in 33 clinics. MMH, masked morning hypertension; PCH, poorly controlled hypertension; WCH, well-controlled hypertension; WCHT, white-coat hypertension. Reproduced with permission from* Circulation *2003;* ***108****:72e–73e.*

ABPM also demonstrated similar results in 240 medicated hypertensive patients. Good clinic BP control of greater than 140/90 mmHg was found in 53 cases (22%). The proportion of patients presenting with high BP became even greater during the second hour after waking (62% in patients with good BP control and 82% in those with poor BP control).

Thus, considering these results in a large number of antihypertensive patients receiving treatment, it is shown that BP values remain high during the early morning hours. At least half of patients with apparently well-controlled office BP do not have their BP under control for the period shortly after waking in the morning.

Morning BP should be monitored to diagnose undetected morning hypertension, even in hypertensive patients who appear well

controlled in the clinic. Management of BP, guided by morning BP levels, could achieve additional benefits in the prevention of target organ damage and cardiovascular events.

Home blood pressure monitoring

Home BP monitoring cannot directly assess morning BP surge, however, combining evening BP (measured just before going to bed) and morning BP, additional information can be derived for clinical practice. The use of memory-equipped devices for home BP monitoring is recommended in order to improve reliability. Recently, we developed a new, integrated-program home BP monitoring device with Omron Healthcare, INC (Kyoto, Japan). This device automatically stores daily personal BP data measured three times on each occasion, twice in the morning and once in the evening (just before going to bed), for a period of two years. This integrated BP monitoring device has many programmes and panels that show the individual BP control status from various viewpoints, including average BP levels, diurnal, weekly and seasonal variations.

In the J-MORE pilot study [73], automatic devices were used to monitor home BP twice daily, in the morning before taking antihypertensive medication and in the evening before going to bed, for three consecutive days. On each occasion, two measurements were obtained. In this study, the first BP reading of each pair of the six sets of measurements (morning and evening for three days) was consistently higher by 3.4–3.9 mmHg for SBP and by 1.1–1.7 mmHg for diastolic BP, while the differences between the first and the second pulse rates were less than 1.0 bpm. This suggests that some pressor response occurs during the first measurement of self measured BP. To reduce the effects of this response, the second measurement, or the average of several measurements, may be preferable to assess morning BP.

Data from the same 519 patients were analysed using the morning BP and evening BP derived from the ABPM data, after controlling for baseline characteristics. The morning–evening (ME) average BP was defined as morning SBP plus evening SBP divided by two (10 mmHg increase: RR [95% confidence interval (CI)] = 1.41 [1.19–1.67], p=0.0001) and the ME surge was

defined as morning SBP minus evening SBP (10 mmHg increase: RR [95%CI] = 1.24 [1.08–1.42], p=0.0025). Both the ME average and ME surge were independently associated with the risk of stroke (*see* Table 4.2) [73].

Relative risk of stroke events in hypertensive patients

Systolic pressure (10 mmHg increase)	Relative risk (95% CI)	p-value
ME average	1.41 (1.19–1.67)	0.0001
ME surge	1.24 (1.08–1.42)	0.0025

Table 4.2. *Jichi Medical School Ambulatory Blood Pressure Monitoring study (Wave 1) (n=519). Controlled for age, gender, body mass index, smoking status, diabetes, hyperlipidemia, silent cerebral infarcts and medication status using Cox regression analysis. CI, confidence interval; ME, morning–evening. Reproduced with permission from* Circulation *2003;* ***108****:110e–111e.*

Definition of morning hypertension

As stated earlier, there is no consensus on the definition of morning hypertension. The JMS ABPM study (Wave 1) temporarily defined the morning (predominant) hypertension based on self-measured home BP level in the morning and evening (before going to bed), as shown in Figure 4.2.

- Average morning–evening BP (Av-ME-BP) was defined as: (morning BP + evening BP)/2.
- Morning–evening BP difference (Di-ME-BP) was defined as: morning BP – evening BP.

The American Society of Hypertension and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) guidelines recommend 135/85 mmHg as the cut-off value of the averages of several home BP levels or daytime ambulatory BP levels to distinguish WCHT from 'true' hypertension (*see* Table 4.3) [75,76].

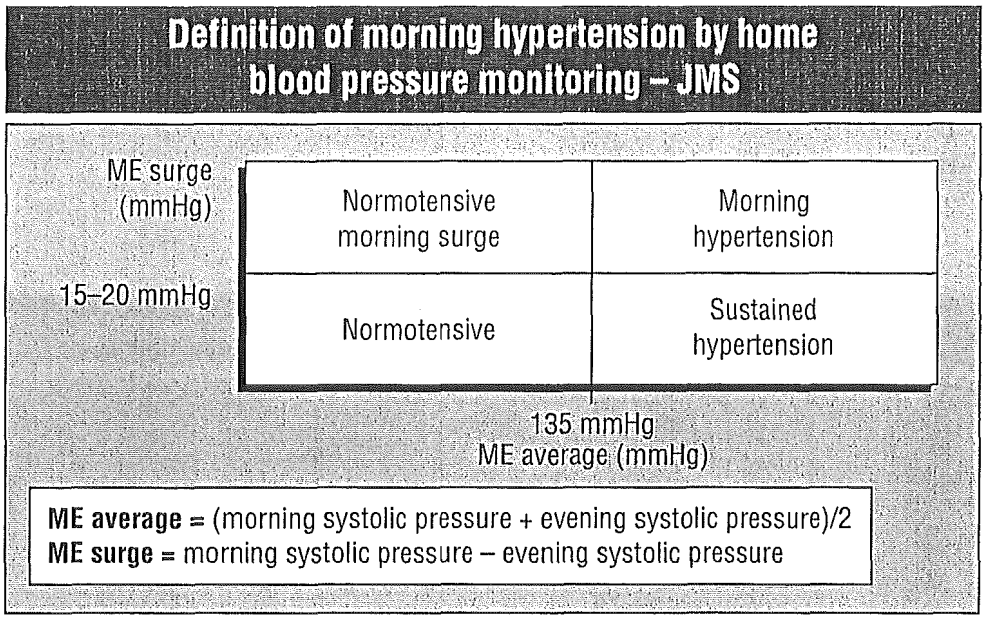

Figure 4.2. *JMS, Jichi Medical School; ME, morning–evening.*

Ambulatory BP level and hypertension status (American Society of Hypertension Expert Panel)

	Normal	Borderline	Abnormal
Systolic BP			
Awake	<135	135–140	>140
Sleep	<120	120–125	>125
24-hour	<130	130–135	>135
Diastolic BP			
Awake	<85	85–90	>90
Sleep	<75	75–80	>80
24-hour	<80	80–85	>85

Table 4.3. *BP, blood pressure. Reproduced with permission from* Am J Hypertens *1996; 9:1–11.*

In the JMS ABPM study (Wave 1), both Av-ME-BP and Di-ME-BP appear to be independent predictors of stroke events in elderly hypertensive patients. As the cut-off value of the top quartile of Di-ME-SBP was 20.8 mmHg, a cut-off value of 20 mmHg was used.

Patients were classified into four groups according to their Av-ME-BP and Di-ME-BP. Firstly, the sustained hypertension group, where the Av-ME-SBP was greater than 135 mmHg or the WCHT group, where the Av-ME-SBP was less than 135 mmHg. Secondly, whether there was a higher BP in the morning than in the evening, that is, a Di-ME-SBP of more than 20 mmHg, or not (a Di-ME-SBP of less than 20 mmHg) (*see* Figure 4.3).

In this preliminary study, in medicated hypertensive patients the left ventricular mass index (LVMI) was assessed (using echocardiography) in the four defined groups and was shown to be highest in the morning (predominant) hypertension group [77]. Within the two WCHT groups (both with Av-ME-SBP <135 mmHg), WCHT + Di-ME-BP 15 mmHg or more had a significantly higher LVMI than the WCHT + Di-ME-BP 15 mmHg or less group.

Another Japanese study also found similar results. Unmedicated hypertensive patients with Di-ME-BP of more than 10 mmHg (n=61) had a higher LVMI than those with Di-ME-BP of less than 10 mmHg (n=157) (130+25 versus

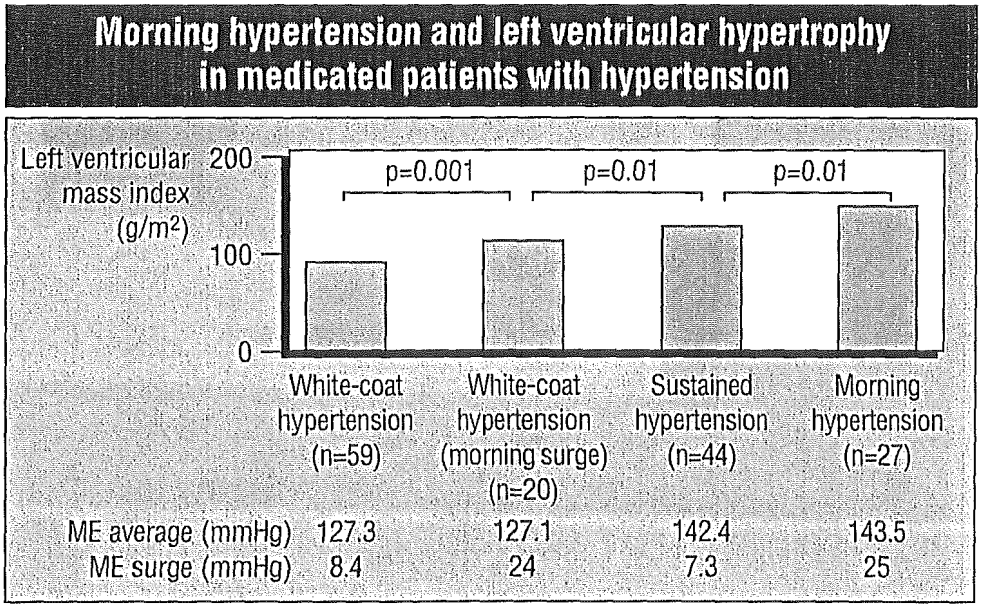

Figure 4.3. *ME, morning–evening. Data presented at the 2003 Annual Scientific Meeting of Japanese Society of Hypertension, Miyazaki, Japan.*

100+15 g/m^2, p<0.0001) [78]. In addition, in medicated hypertensive patients well-controlled for evening SBP of less than 135 mmHg, those patients with a Di-ME-BP of more than 10 mmHg (n=46) still had a higher LVMI than those patients with a Di-ME-BP of less than 10 mmHg (n=93) (126+18 versus 98+18 g/m^2, p=0.003) [78].

Ambulatory blood pressure monitoring

Theoretically, there are two types of morning hypertension (*see* Figure 4.4) [79]. The first is morning BP surge type – in the JMS ABPM study (Wave 1), the morning surge group exhibited morning hypertension (mean morning SBP level >170 mmHg) [43]. The other is riser/nondipper (nocturnal hypertension) type with persistent high BP from night-time to morning. As described above, both types appear to be at risk for cardiovascular disease, independent of each other. Self-measured home BP monitoring is

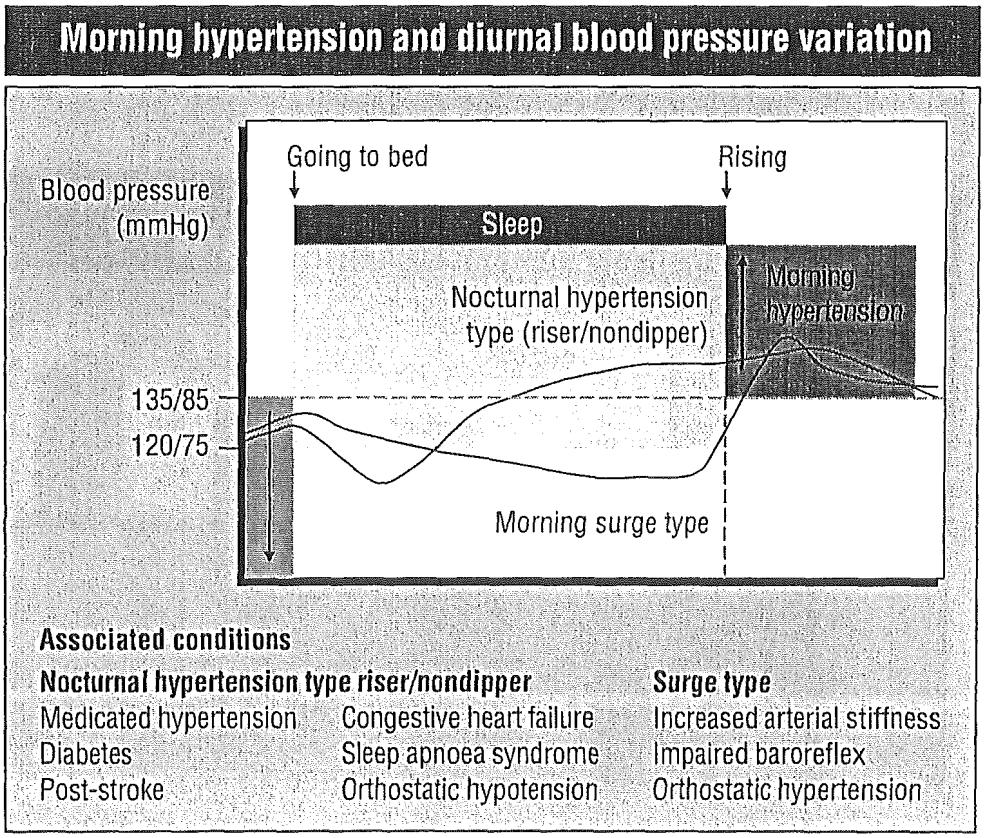

Figure 4.4

useful in identifying morning hypertension; however, only ABPM can measure BP levels at night during sleep. Thus, ABPM can assess nocturnal dipping status and distinguish between the types of morning hypertension [80].

In addition, ABPM could be used to evaluate not only BP behaviours outside of a clinical setting, but also BP variability during daily activities [81]. Ambulatory BP variability during specific stress, such as orthostatic stress or physical and psychological stress, which might be related to future hypertension, target organ damage and cardiovascular events, could be assessed by ABPM (*see* Figure 4.5) [82,83]. Some of these conditions overlap with each other because impaired baroreceptor sensitivity is partly involved in their pathogenic mechanisms. For example, hypertensive patients with orthostatic hypertension had higher morning SBP levels of approximately 10 mmHg than those without this condition (*see* Figure 4.6) [84].

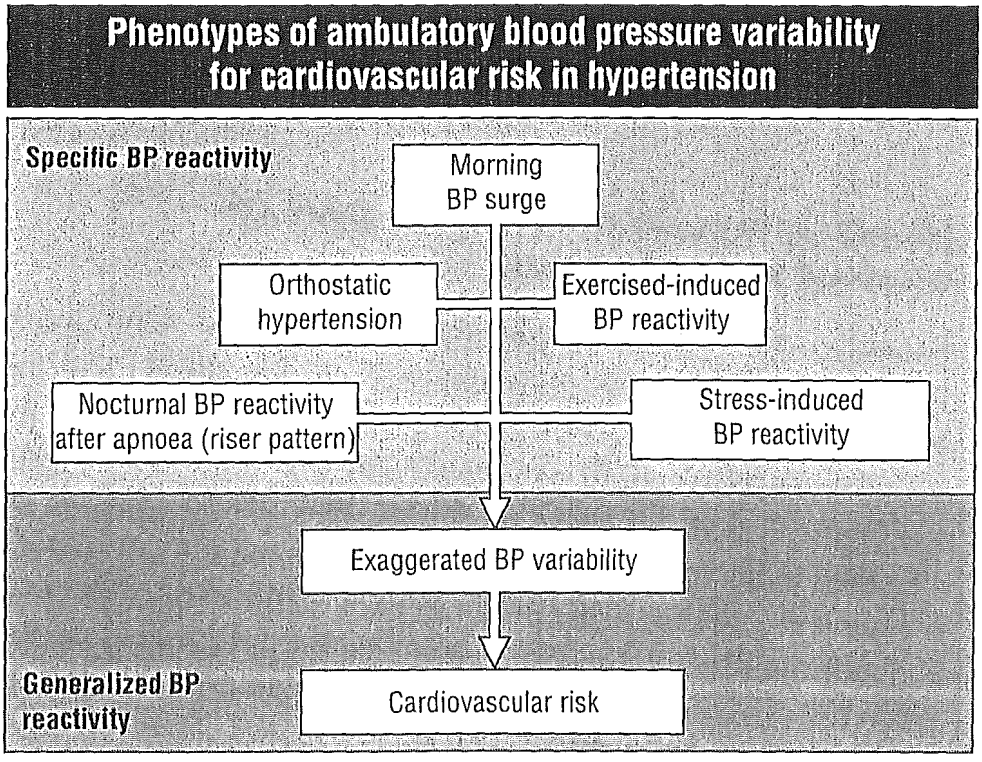

Figure 4.5. *BP, blood pressure. Reproduced with permission from* Am J Hypertension *2004; 17:1075–1076.*

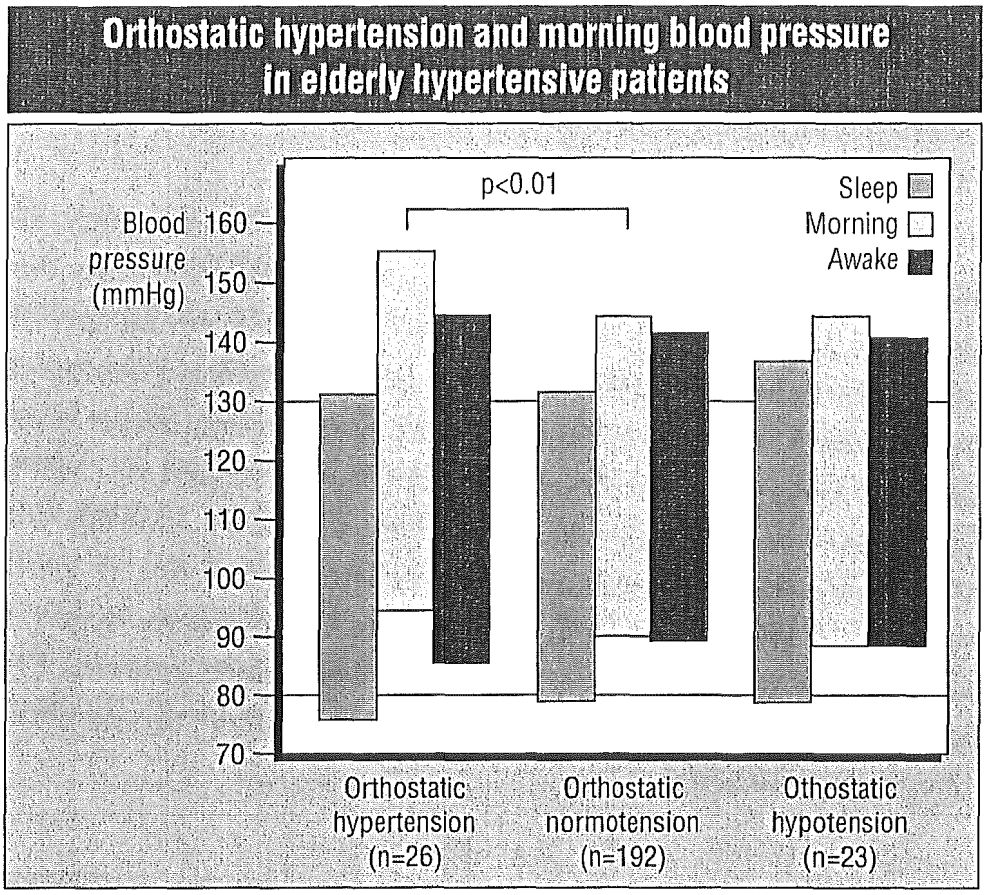

Figure 4.6. *Reproduced with permission from* J Am Coll Cardiol *2002;* ***40****:133–141.*

Morning hypertension as a part of masked hypertension

Recently, the clinical implications for patients with masked hypertension, who are normotensive in the clinic, but have increased BP in daily life, have attracted attention [85]. In a recent prospective study on elderly patients, those with masked hypertension had the same cardiovascular risk as patients with sustained hypertension [86]. In other recent studies in hypertensive patients taking medication, patients with masked hypertension had significantly poorer cardiovascular prognosis than those with well-controlled home [87] or ambulatory BP levels [88] independent of clinic BP.

Morning hypertension, when the clinic BP is normal, is just one facet of masked hypertension (*see* Figure 4.7). Others include

nocturnal hypertension, when a high nocturnal BP level carries over into a high morning BP level, which can overlap with morning hypertension and stress-induced hypertension and would only be detected by ABPM.

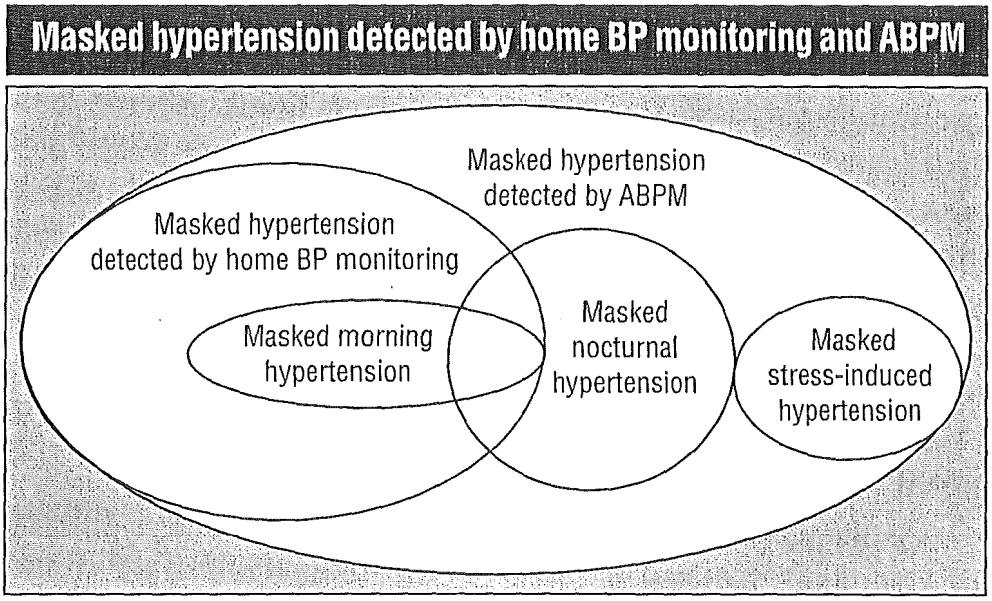

Figure 4.7. *BP, blood pressure; ABPM, ambulatory blood pressure monitoring.*

5

Controlling morning hypertension

Home blood pressure monitoring/guided morning hypertension control

Strict BP control during a 24-hour period provides important protection against target organ damage and the most effective prevention for cardiovascular disease. In addition, specific antihypertensive therapy targeting morning hypertension would provide additional protection at the time of the greatest risk, that is, the morning hours. Recently, the development of once-daily dosing antihypertensive agents, now widely used as standard antihypertensive medication, has decreased the patient burden and contributed to increased patient compliance. However, as shown in Figure 4.1 [72], current standard antihypertensive medication is insufficient for controlling morning hypertension.

As the pressor mechanism of morning hypertension is different in each individual patient, home BP monitoring/guided BP control is recommended for the management of morning hypertension. Controlling both the ME average and the ME surge is important; target BP control levels for ME average are less than 135/85 mmHg. In addition, although there is no conclusive evidence, theoretically, it appears preferable to reduce the ME surge to its target level of less than 15 mmHg. Finally, absolute morning BP levels of less than 135/85mmHg would be ideal. Usually, combined therapy of specific and nonspecific antihypertensive medication is required to control morning hypertension sufficiently. Monitoring ME average and ME surge using home BP monitoring is a useful assessment of the effectiveness of individual antihypertensive medication.

Specific versus nonspecific antihypertensive treatment

Figure 5.1 shows the vector of specific antihypertensive medication (towards the baseline) and that of nonspecific medication (towards the left). Nonspecific medication for morning BP includes long-acting calcium antagonists, such as amlodipine, and diuretics. The longer acting the antihypertensive, the better it is at controlling

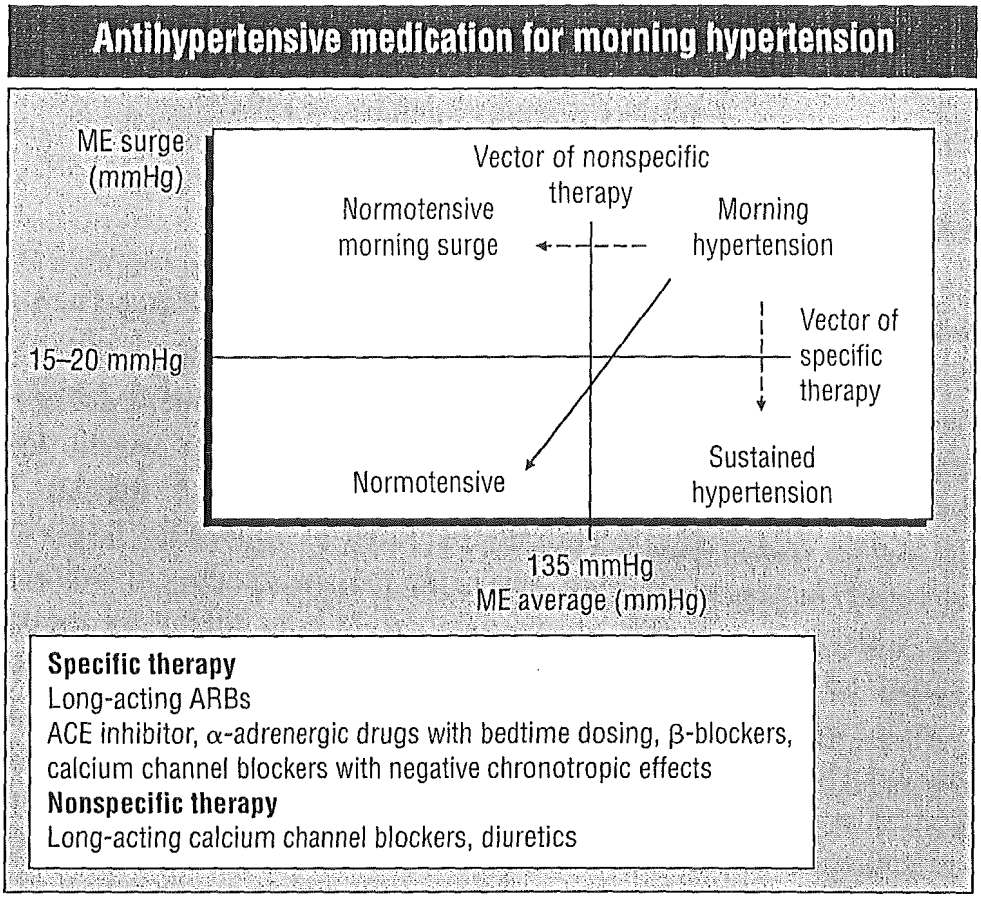

Figure 5.1. *ME, morning–evening; ARB, angiotensin-receptor blockers; ACE, angiotensin-converting enzyme.*

morning BP. These drugs are usually administered once daily in the morning and they provide continuous BP reduction over a 24-hour period to attenuate exaggerated morning BP surge. In addition, more specific chronological treatment for morning BP surge may be achieved using an antihypertensive medication that reduces the pressor effect of the neurohumoral factors potentiated in the morning, such as inhibitors of sympathetic activity or the RAAS.

Characteristics of each class of antihypertensives

Diuretics

Diuretics provide a long duration of BP lowering effect and their effectiveness for the prevention of cardiovascular events is well

established. However, when morning hypertension is treated using diuretics, nondippers shift towards becoming dippers, while the dipping pattern of dippers remains unchanged [89].

Calcium antagonists

Calcium antagonists have potent BP lowering effects on morning BP when their effect persists for 24 hours. ABPM was performed before and after once-daily dosing of valsartan (valsartan group, n=38) and amlodipine (amlodipine group, n=38) in 76 hypertensive patients. Valsartan was titrated from 40 mg/day to 160 mg/day (mean dose 124 mg/day) and amlodipine was titrated from 2.5 mg/day to 10 mg/day (mean dose 6.4 mg/day) in order to achieve the target BP of 140/90 mmHg or less [90]. The antihypertensive effect of amlodipine was superior to that of valsartan on 24-hour SBP (–14 mmHg versus –7 mmHg, p=0.008). In addition, amlodipine significantly reduced morning SBP from 156 to 142 mmHg (p<0.001) but valsartan did not. Reduction in morning SBP surge (morning SBP minus the lowest night SBP) was significantly greater in patients treated with amlodipine compared with those treated with valsartan (–6.1 mmHg versus +4.5 mmHg, $p \leq 0.02$). Thus, amlodipine monotherapy was more effective than valsartan monotherapy in controlling 24-hour ambulatory BP and morning BP in hypertensive patients. In addition, the prevalence of nonreactor patients (showing no reduction on morning BP) was significantly lowered in the amlodipine-treated group than in the valsartan-treated group (*see* Figure 5.2).

Some calcium antagonists have specific modes of action and could therefore provide more specific medication. The specific T- and N-type calcium antagonist, cilnidipine, which inhibits catecholamine release is a possible candidate [91]. Azelnidipine, another calcium antagonist, lowers the heart rate significantly when compared with amlodipine. In addition, pharmacokinetically, some extended-release forms of verapamil could also achieve effective BP reduction in the morning [92].

Alpha-adrenergic blockers and alpha/beta-adrenergic blockers

Alpha-adrenergic and alpha/beta-adrenergic blockers are effective in reducing morning BP surge in hypertensive patients. In

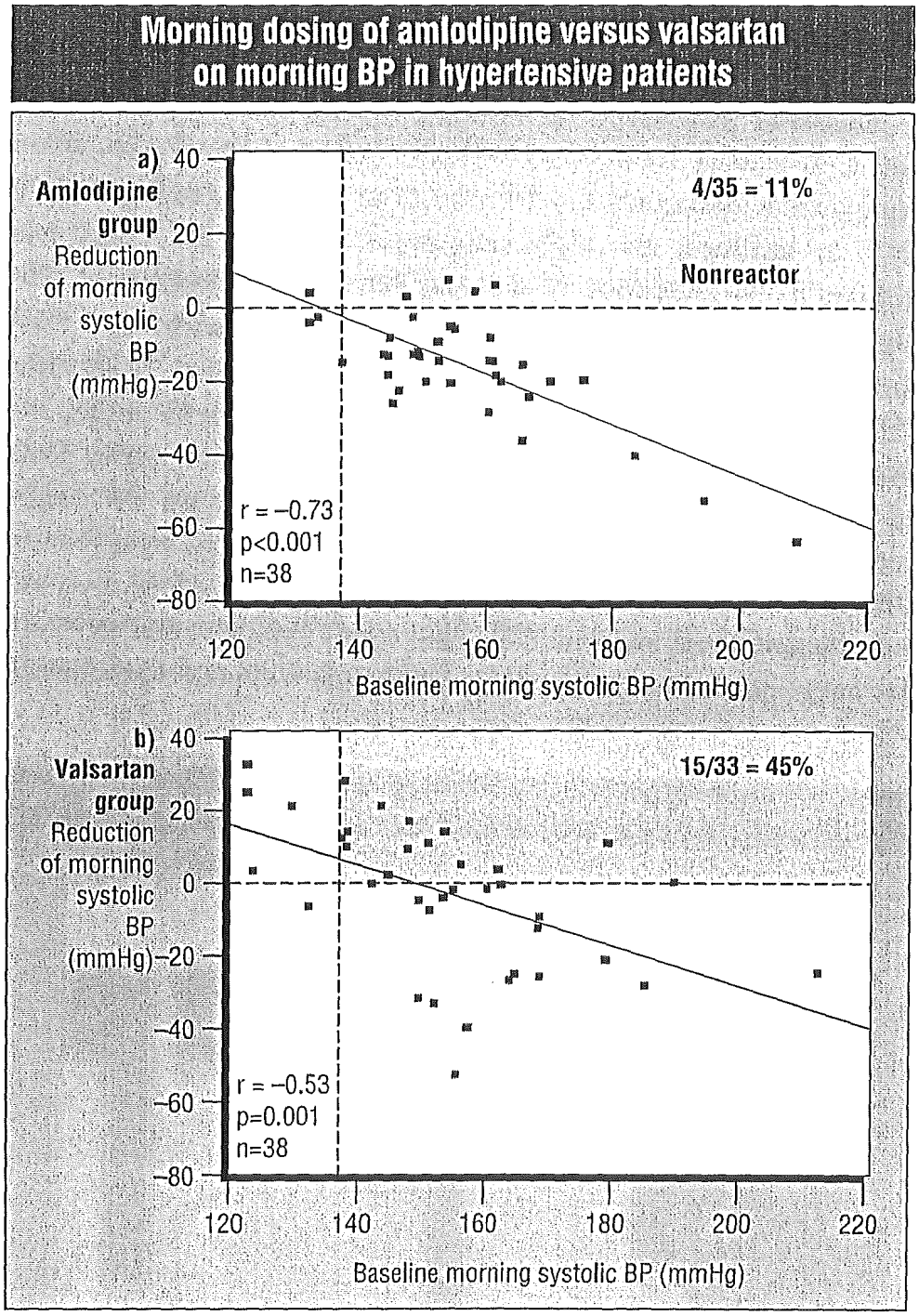

Figure 5.2. *Nonreactors in the valsartan group were 4.1 times more common. BP, blood pressure.*

particular, night-time dosing of alpha-adrenergic blockers achieves peak effect in the mornings, providing greater BP reductions during these hours. In the Hypertension and Lipid Trial