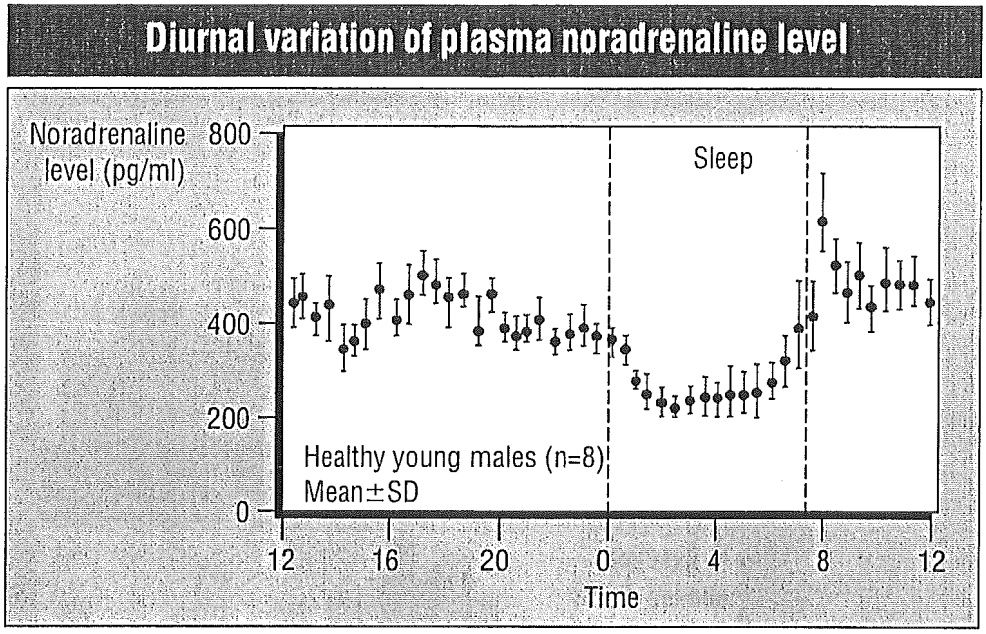

Figure 1.2. *SD, standard deviation. Reproduced with permission from* J Clin Endocrinol Metab *1985;* ***60****:1210–1215.*

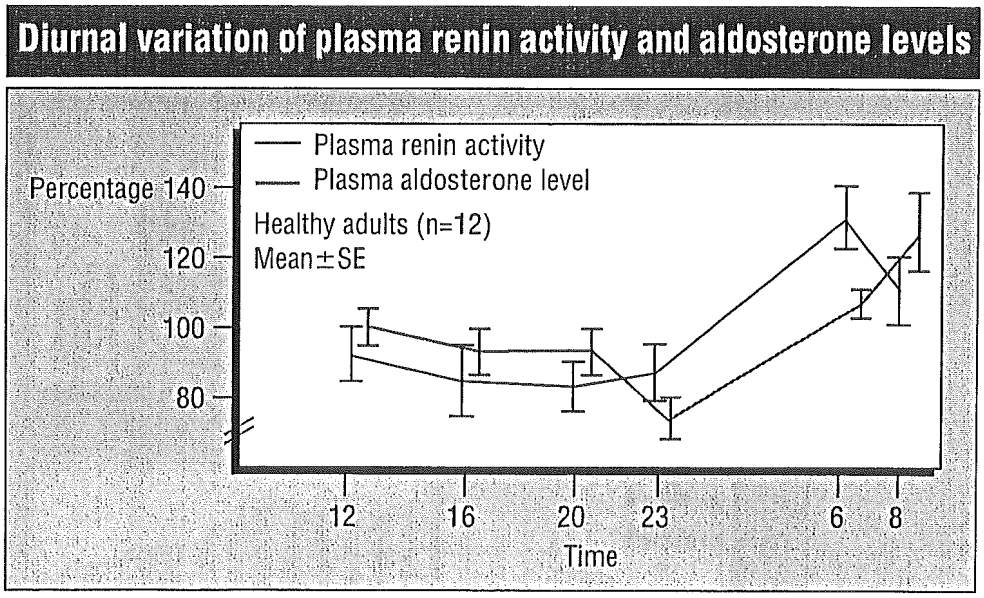

Figure 1.3. *SE, standard error. Reproduced with permission from* Horm Metab Res *1990;* ***22****:636–639.*

pattern [13–22]. The frequency of this nondipping pattern increases with age, reaching approximately 50% in elderly patients. In the recent Jichi Medical School Ambulatory Blood Pressure Monitoring (JMS ABPM) study (Wave 1) the nondipper

subgroup was defined using a value of a nocturnal reduction in BP of 10% of waking level.

In addition, this study subclassified four dipping states according to the degree of nocturnal falls in BP, including two extreme subtypes:

- risers – with higher nocturnal BP levels than daytime BP; and
- extreme-dippers – with excessive nocturnal BP falls (>20% reduction during night) (*see* Figure 1.4 and Table 1.1).

Risers have the worst prognosis for all the cardiovascular diseases [19–21]; in the JMS ABPM study (Wave 1), risers had a significantly higher prevalence of silent cerebral infarcts, detected by brain magnetic resonance imaging (MRI), than normal dippers [18]. This specific target organ, the brain, had higher relative risk of 4–10 times for clinical stroke events [23]. In fact, during the follow-up period, risers had the worst clinical stroke events, particularly fatal stroke events (*see* Figure 1.5) [20]. In the subtype analysis,

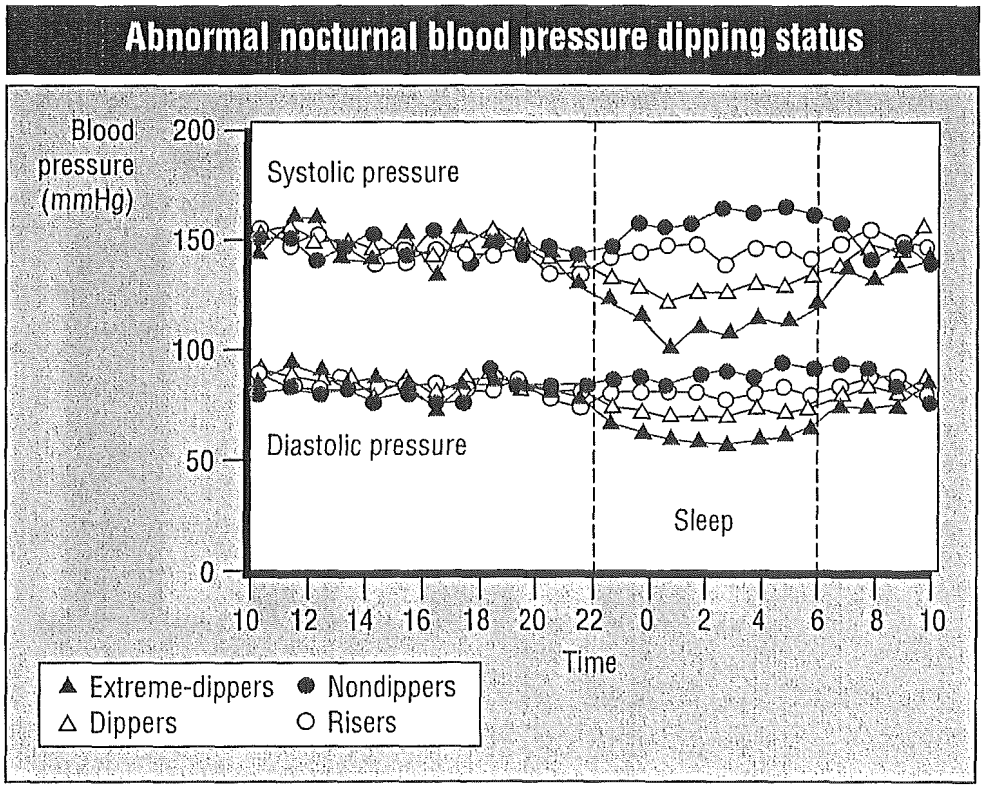

Figure 1.4. *Reproduced with permission from* Hypertension *2001; **38**:852–857.*

Definition of nocturnal BP dipping status

Sleep BP = Average of BPs during sleep period (from the time of going to bed to the time of arising)

Awake BP = Average of BPs during awake period (other period)

Nocturnal BP fall (%) =100 x (1 – Sleep BP / Awake BP)

Definition of four nocturnal BP dipping statuses:

Subtypes	Nocturnal BP fall (%)
Extreme-dippers	>20%
Dippers	10–20%
Nondippers	0–10%
Risers	<0%

Table 1.1. *BP, blood pressure.*

Stroke incidence in hypertensive patients with different dipping statuses of nocturnal blood pressure

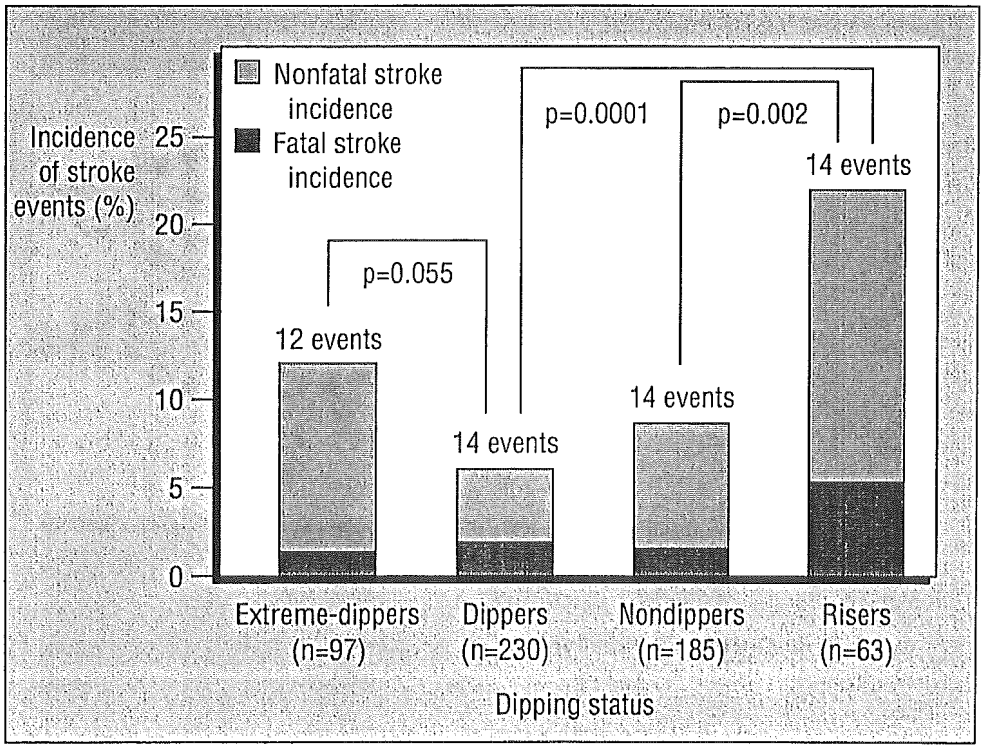

Figure 1.5. *There were a total of 54 events, 35 (65%) ischaemic, 7 (13%) haemorrhagic, 12 (22%) unknown. Jichi Medical School ABPM study (Wave 1).*

haemorrhagic stroke was more common in risers [20]. In addition to stroke events, risers also had a significantly higher risk for cardiac events, including sudden cardiac death (*see* Figure 1.6) [21].

Mechanism of action in nondippers and risers

The mechanism of action controlling nocturnal BP levels in nondippers and risers remains unclear and is different in each patient. Various medical conditions listed in Table 1.2 are associated with nondipping nocturnal BP patterns [22].

The nondipping pattern is clearly associated with increased intravascular volume and salt sensitivity [24]. The nondipper pattern has been reported in secondary hypertensive patients with endocrine abnormalities and in those with autonomic nervous

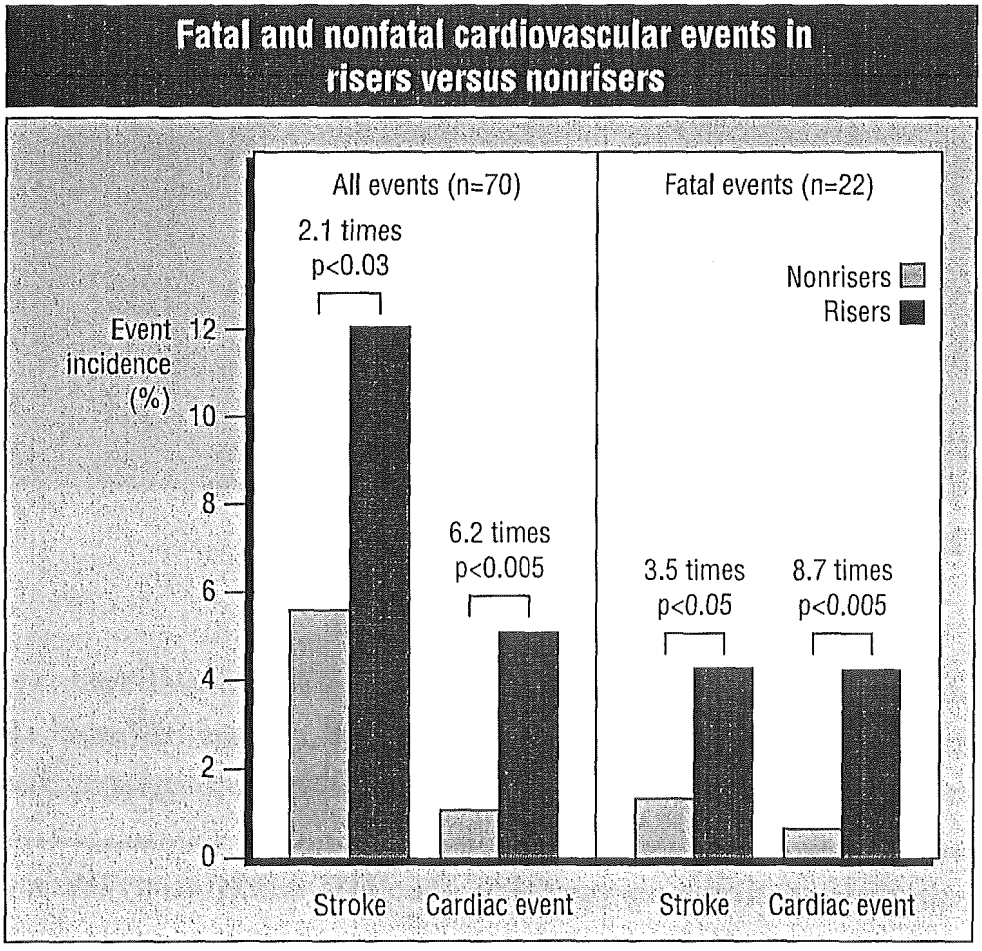

Figure 1.6. *Jichi Medical School ABPM study (Wave 1).*

Associated conditions with abnormal nocturnal blood pressure dipping status
Nondipper/riser
Increased intravascular volume (congestive heart failure, renal failure)
Abnormal autonomic nervous system, diabetes, parkinsonism, Shy–Drager syndrome, cardiac transplantation, orthostatic hypotension, etc.
Secondary hypertension (primary aldosteronism, Cushing syndrome, pheochromocytoma)
Salt sensitivity
Poor sleep quality
Sleep disorders of breathing, such as sleep apnoea
Metabolic syndrome (obesity)
Depression
Impaired cognitive function
Elderly patients
Black patients
Advanced hypertensive target organ damage (silent cerebral infarcts, deep white matter lesion, cardiac hypertrophy, microalbuminuria)
Extreme-dipper
Elderly patients
Orthostatic hypertension
Morning blood pressure surge
Alpha-adrenergic hyperactivity?
Dehydration?
Increased aortic stiffness?

Table 1.2

abnormalities, such as diabetic neuropathy and Shy–Drager syndrome [25]. Studies using power spectral analysis of heart rate variability, obtained with 24-hour Holter electrocardiography, have shown that the diurnal fluctuation of autonomic nervous activity was diminished in nondippers [26]. The JMS ABPM study (Wave 1) also demonstrated that sympathetic nervous activity is lower during the night in extreme-dippers and lower during the daytime in

nondippers, who show a diminished increase of parasympathetic nervous activity during the night [27]. Orthostatic changes in BP and neurohumoral factors are also partly associated with abnormal nocturnal dipping status in elderly hypertensive patients [28,29] and risers are likely to have orthostatic hypotension [28]. The effects of night-time dosing of an alpha$_1$-adrenergic blocker, doxazosin, on mean nocturnal systolic BP (SBP) change include decreases of 0.7 mmHg in dippers, 12 mmHg in nondippers and 18 mmHg in risers; the reduction was only significant in the latter two groups (both $p<0.01$) [30]. These results indicate that the abnormal diurnal BP variations are closely related to abnormalities of autonomic nervous activity.

Patients with sleep disorders or breathing difficulties, such as sleep apnoea, are likely to have a nondipping pattern of nocturnal BP. Increased frequency of microarousals and related sympathetic activation, due to nocturnal hypoxia, may contribute to the nondipping pattern [31]. Recent results show that nocturnal physical activity was increased in nondippers compared with those with a normal nocturnal fall in BP [32]. This increased physical activity may be due, in part, to nocturnal behaviour (going to the bathroom, getting a drink of water, etc.) and poor sleep quality. It may also be possible that increased physical activity reflects poor sleep quality and an increased frequency of unconscious microarousals will trigger sympathetic activation. There is also the possibility that increased nocturnal physical activity *per se* activates autonomic nervous function to modulate endocrine function [33]. These studies indicate that a change of the sleep quality using hypnotics or antidepressants could affect nocturnal falls in BP and, therefore, the development of silent and clinically overt cerebrovascular disease. Thus, improvement of sleep quality together with a reduction of nocturnal physical activity may result in a more normal diurnal rhythm, especially in nondippers [33]. This could also reduce the risk of cardiovascular disease in elderly patients.

There are currently no studies on the association between nocturnal fall in BP and the onset time of cardiovascular events; however, there is the possibility that diurnal variation in onset time of cardiovascular events may be reduced in nondippers. In depressed patients, nocturnal onset of acute myocardial infarction is significantly more

common [34]; also, diabetic patients exhibit less significant diurnal variation of the onset time of acute myocardial infarction [35]. Subclinical depression, a newly recognised cardiovascular risk factor, is associated with poor sleep quality. In a recent study, it was found that depression in men is associated with a disrupted diurnal BP variation (a tendency towards the nondipping pattern), which was independent of changes in physical activity [36].

Extreme-dippers

In addition to nondippers or risers, there is another subclassification of patients – extreme-dippers. These patients have a more marked nocturnal fall in BP than dippers (another subtype of abnormal diurnal BP variation) [18] and among elderly patients with sustained hypertension it was found that extreme-dippers had an intermediate risk for clinical stroke, particularly nonfatal stroke, compared with dippers (*see* Figure 1.5) [20]. In addition, silent cerebral infarcts, detected by brain MRI at baseline, are more common in extreme-dippers than dippers, indicating that extreme-dippers may be at risk for nonfatal lacunar strokes [20]. Also, extreme-dippers can have increased arterial stiffness with reduced circulating blood volume, in addition to an excessive increase in orthostatic BP and morning surge due to alpha-adrenergic hyperactivity [18,22,28,29]. For these patients, individualized therapy based on ambulatory BP could spare the silent hypertensive target organ damage and clinical cardiovascular consequences that result from excessive BP variability [37–41]. In fact, in extreme-dippers, antihypertensive therapy has been shown to increase the myocardial ischaemic episodes during the night that are associated with coronary artery stenosis [42]. Further studies are necessary to confirm the clinical implications of extreme-dipping and its management.

2

Morning surge in blood pressure

Morning BP surge is one of the components of diurnal BP variation and is partly associated with nocturnal BP dipping status. Morning surge may be an important factor in cardiovascular disease, as both clinical and silent events of the heart and brain occur most frequently during the morning period (*see* Figure 1.1) [1–8]. The extent to which the morning BP surge is a direct cause of cardiovascular disease is still to be proven, but a clear association has been demonstrated. Excessive morning BP surge appears to be a risk factor for cardiovascular disease, particularly in older hypertensive patients with impaired autoregulation of hypertensive target organs [43,44].

Definition of morning blood pressure surge

There is no consensus on the definition of the morning BP surge. A recent study defined the 'sleep–trough surge' as the morning SBP minus the lowest SBP during sleep (*see* Figure 2.1) [44]. The

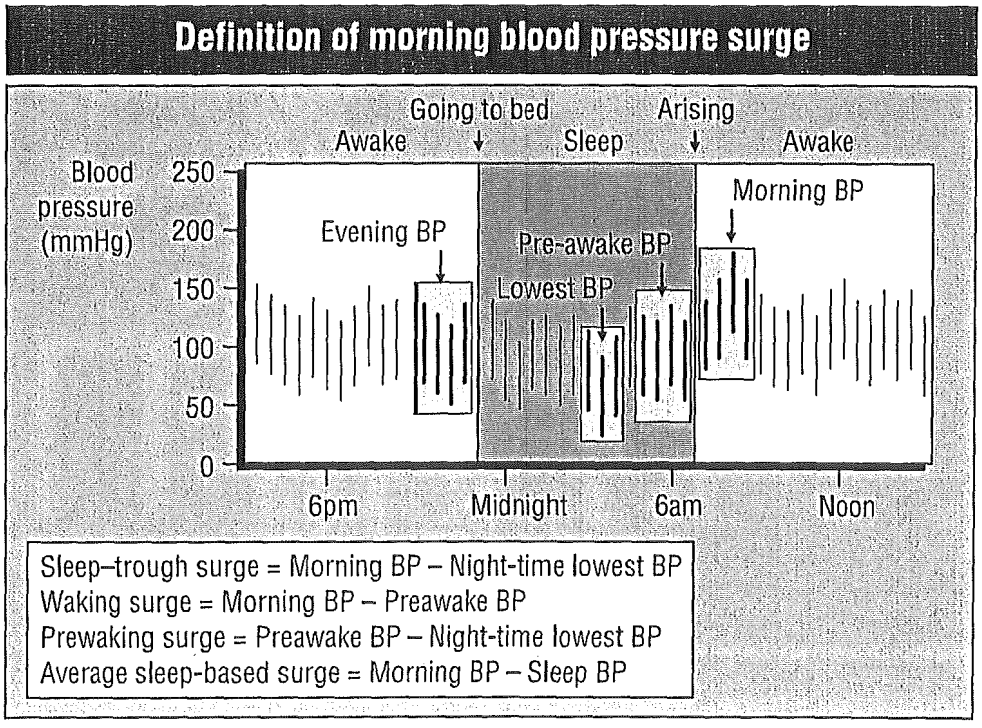

Figure 2.1. *BP, blood pressure. Jichi Medical School ABPM Study (Wave 1). Reproduced with permission from* Circulation *2003;* ***107****:1401–1406.*

sleep–trough surge consists of two surges: the waking morning BP surge, defined as the morning SBP minus the pre-awake SBP, and the prewaking morning BP surge, defined as the prewaking SBP minus the lowest SBP. The prewaking surge is associated with sleep quality, while the waking surge appears partly associated with impaired baroreceptor reflex. Morning BP was defined as the average BP during the first two hours after waking (four BP readings). The lowest BP was defined as the average BP of three readings centred on the lowest night-time reading (ie, the lowest reading plus the readings immediately before and after). The mean±standard deviation (SD) sleep–trough surge in the total sample was 34±18 mmHg. As the cut-off value for identifying the top decile (the surge group) was

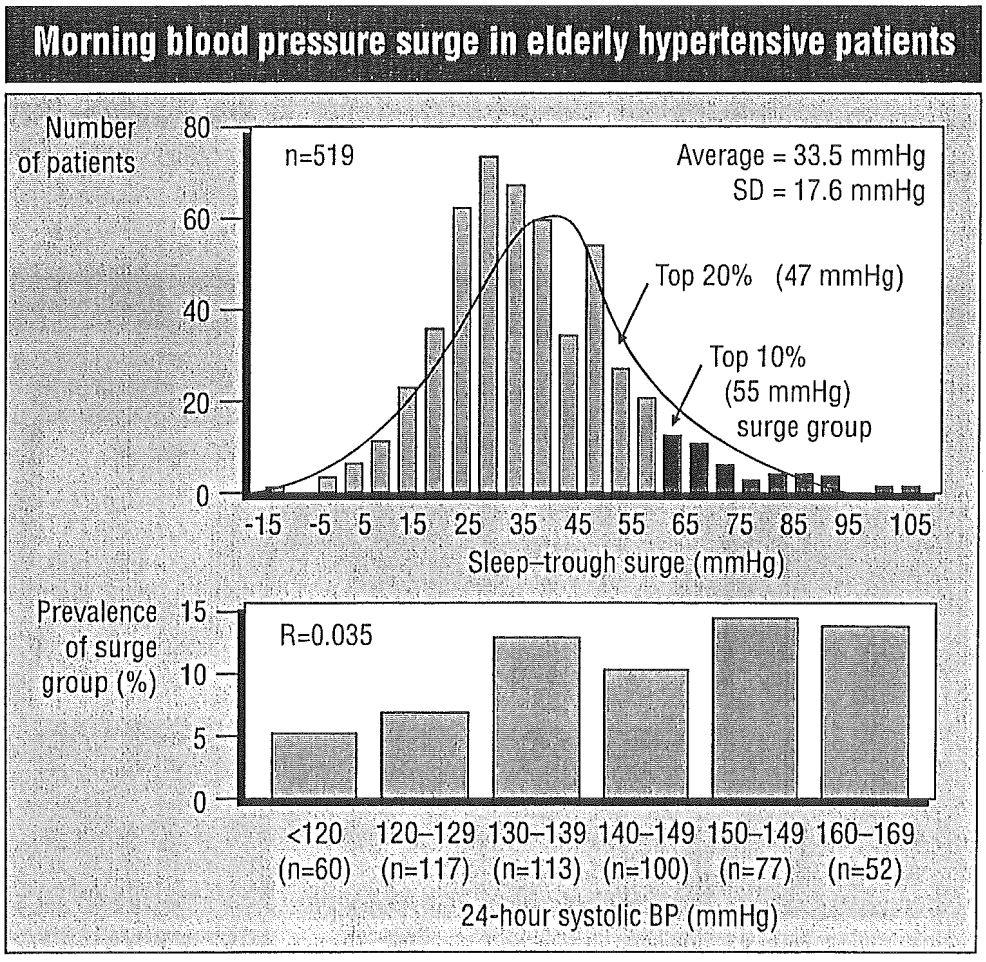

Figure 2.2. *SD, standard deviation; BP, blood pressure. Jichi Medical School ABPM Study (Wave 1). Reproduced with permission from* Circulation *2003;* ***107****:1401–1406.*

55 mmHg (*see* Figure 2.2, upper figure) the patients were subclassified according to the extent of the sleep–trough surge; the top decile of sleep–trough surge (>55 mmHg, n=53; the morning surge group) versus all others (n=466, the nonsurge group). The ambulatory BP levels of the two groups are shown in Figure 2.3. The surge group exhibited higher morning BP levels (morning hypertension) than the nonsurge group.

Advancing age and increases in 24-hour BP levels are significant determinants of excessive morning BP surge. In the sample of older hypertensive patients, the surge group was more common in the higher 24-hour BP subgroups (*see* Figure 2.2, lower figure). However, it must be noted that other authors use other definitions: some authors define morning BP surge as morning SBP level measured on standing minus SBP before rising. This definition is relatively similar to that of waking surge, as previously described. Some authors define morning BP surge as peak BP or the average BP during morning period minus average BP during the sleep period.

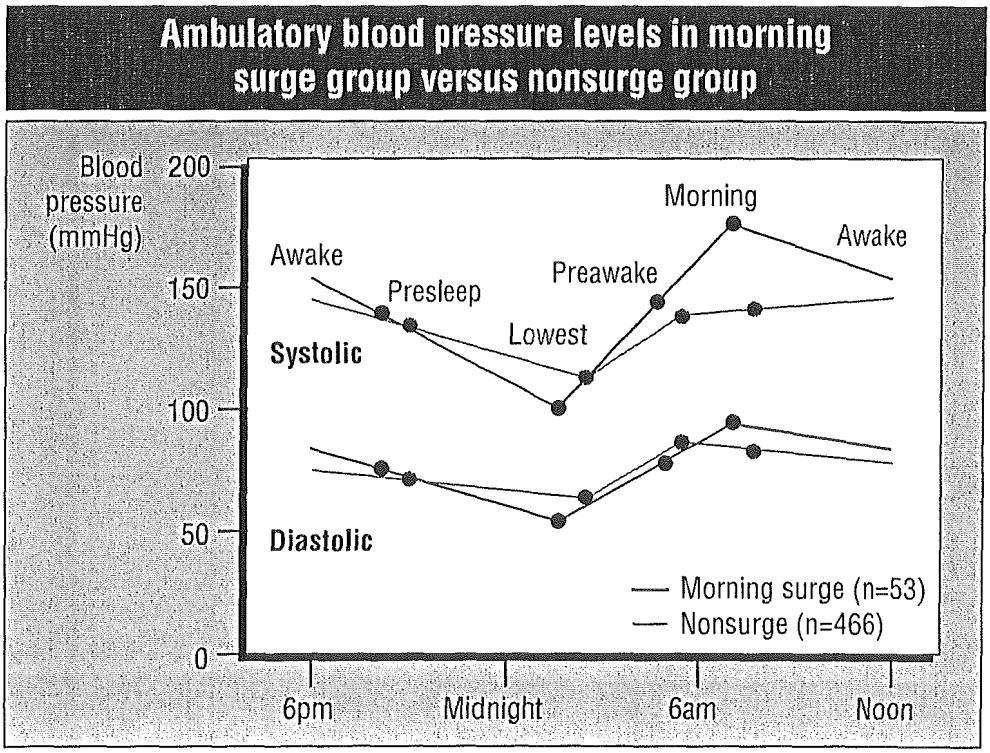

Figure 2.3 *Jichi Medical School ABPM study (Wave 1). Reproduced with permission from* Circulation *2003;* ***107****:1401–1406.*

Cardiovascular events

There are two relatively small prospective studies to support the possible risk of morning BP surge. The first is the JMS ABPM study (Wave 1) carried out in elderly hypertensive patients [44] and the other is a French study of hypertensive patients [45]. In the JMS ABPM, a prospective study of 519 hypertensive patients (mean age: 72 years) [44], brain MRI was conducted to assess silent cerebrovascular disease together with 24-hour ABPM at baseline. The prognosis for stroke was studied during the follow-up period of 41 months.

Both the sleep–trough surge and waking surge were significantly associated with stroke risk in this study. Nonsurge patients were matched for age (range: two years) and 24-hour SBP level (range: 4 mmHg) to morning surge patients and control subjects were weighted to simulate a balanced design (*see* Table 2.1). Clinical stroke events occurred more frequently in the morning surge group

Morning blood pressure surge and silent and clinical cerebrovascular disease

	Morning surge group (n=46)	Nonsurge group (n=145)	p-value
Age (years)	76	76	NS
24-hour systolic BP (mmHg)	142	142	NS
Baseline data			
Silent cerebral infarct			
Prevalence (%)	70	49	0.02
Number (/per person)	2.0	1.5	0.01
Multiple cerebral infarcts			
Prevalence (%)	54	37	0.04
Prospective data			
Stroke incidence (%)	17	7.0	0.04
Relative risk = 2.7			

Table 2.1. *Mean or percentages are shown. NS, not significant; BP, blood pressure. Jichi Medical School ABPM study (Wave 1). Reproduced with permission from* Circulation *2003;* ***107****:1401–1406.*

than the nonsurge group; the relative risk (RR) in the morning surge group (versus the nonsurge group), calculated by a weighted Cox regression analysis, remained significant (RR=2.7).

As expected, there was a significant association between nocturnal BP dipping status and excessive morning BP surge; the Cox regression analysis was conducted with both nocturnal BP dipping status and morning BP surge (*see* Table 2.2). Age, 24-hour BP and baseline prevalence of silent cerebral infarcts appeared to be associated with stroke risk and there were no other significant cofactors (gender, body mass index, smoking status, diabetes or hyperlipidaemia). Controlling for the cofactors and dipping status, sleep–trough surge was significantly and independently associated with stroke events and a morning surge in SBP of 10 mmHg increased the clinical stroke risk by 25%. Risers remained a significant predictor of stroke events and the risks associated with extreme-dippers disappeared after morning BP surge was controlled. The risks associated with extreme-dippers appear to be explained, in part, by the excessive morning BP surge in older hypertensive patients, therefore, the morning BP surge could be a significant risk factor for stroke, independent of other cardiovascular

Relative risk for stroke event in hypertension: relation to morning BP surge and nocturnal BP dipping status

	Relative risk (95% CI)	p-value
Morning systolic BP surge (10 mmHg)	1.25 (1.06–1.48)	0.008
Dipping status of nocturnal BP (versus dippers)		0.025
Exreme-dippers	1.43 (0.59–3.43)	0.426
Nondippers	1.76 (0.78–4.01)	0.175
Risers	2.71 (1.02–7.21)	0.047

Table 2.2. *CI, confidence interval; BP, blood pressure. n= 519, adjusted for age, 24-hour systolic BP and silent cerebral infarcts. Jichi Medical School ABPM study (Wave 1). Reproduced with permission from* Circulation *2003;* ***107****:1401–1406.*

risk factors, including age, 24-hour ambulatory BP level, nocturnal BP dipping status and silent cerebrovascular disease.

A recent French prospective study in 507 patients with hypertension also found similar results [45]. Hypertensive patients were divided into quartiles of waking surge using the waking BP surge, defined as morning SBP measured on standing minus SBP before rising. Although there were no significant differences in the 24-hour BP levels between each group, left ventricular hypertrophy (LVH), assessed by echocardiography at baseline, was more advanced and cardiovascular complications occurred more frequently during the follow-up period in the higher quartile groups (*see* Figures 2.4 and 2.5). In the multivariate analysis, waking morning BP surge was significantly associated with cardiovascular risk independent of age and 24-hour BP level.

It is well-known that cardiovascular risk varies during the week; cardiovascular events occur most frequently on a Monday. A large study of the number of consecutive cases of cardiac sudden death

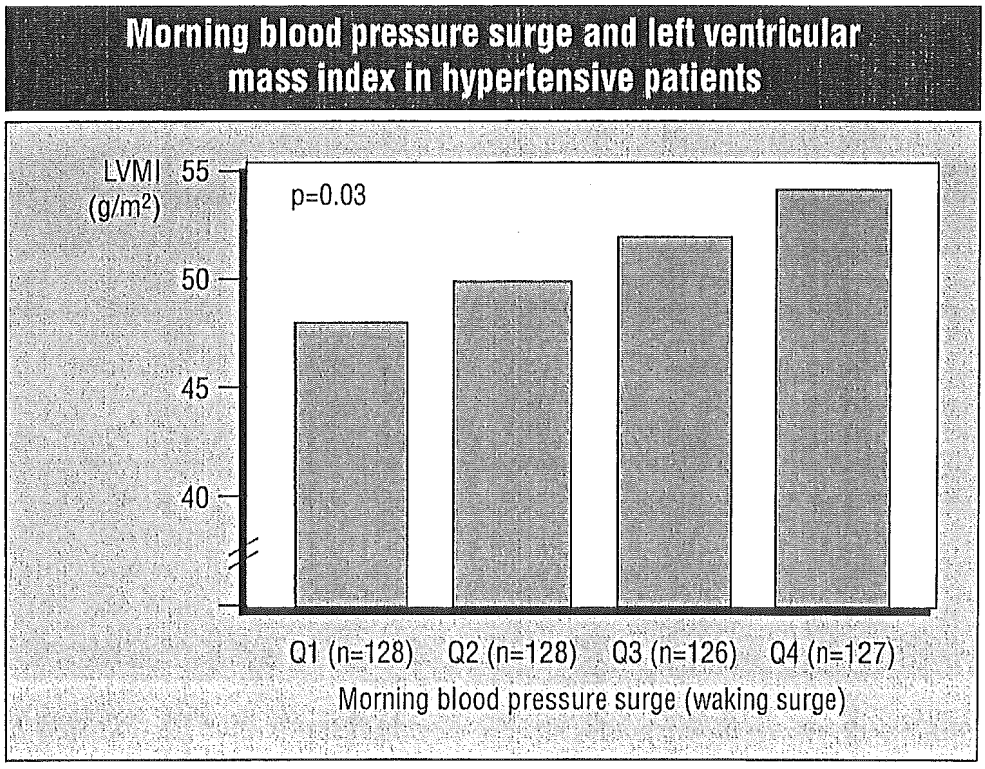

Figure 2.4. *LVMI, left ventricular mass index; Q, quartile. Reproduced with permission from* J Hypertens *2004; **22**:1113–1118.*

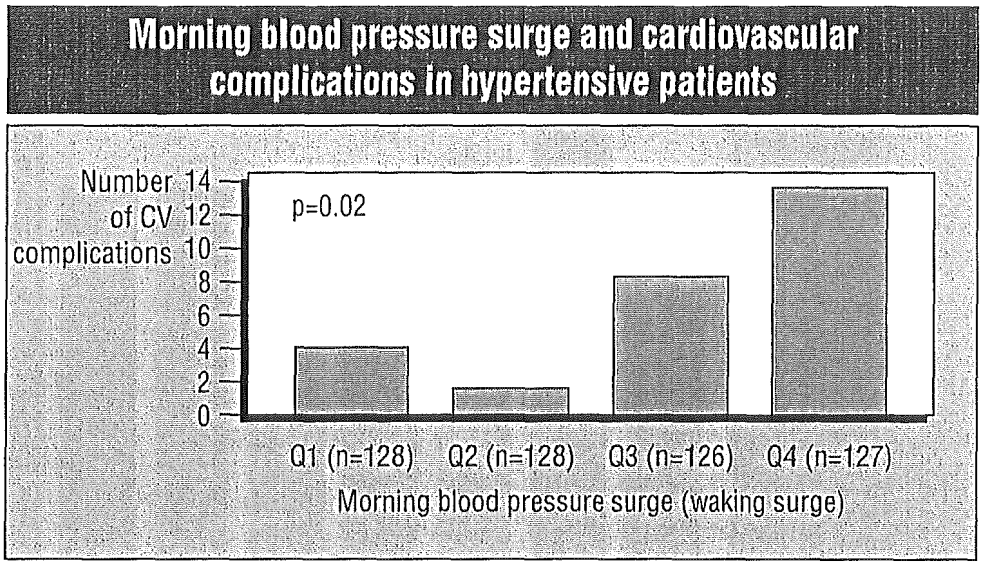

Figure 2.5. *CV, cardiovascular; Q, quartile. Reproduced with permission from* J Hypertens *2004; **22**:1113–1118.*

showed significant weekly variation with a Monday peak (*see* Figure 2.6) [46]. In a recent unique study in which ABPM was conducted for seven days in a community-dwelling population [47], there was significant variation in morning and daytime BP levels during the week, while there was no significant difference in the night-time BP levels. Morning BP level and morning BP surge were highest on Monday (*see* Figure 2.7); this 'Monday morning surge' may contribute to cardiovascular risk.

Hypertensive target organ damage

Morning BP surge is also significantly associated with hypertensive target organ damage. In the JMS ABPM study (Wave 1), silent cerebral infarct was measured by brain MRI at baseline and was more frequently detected in the morning surge group than in the nonsurge group, particularly multiple silent cerebral infarcts (*see* Table 2.1) [44]. Exaggerated morning BP surge also appeared to increase hypertensive heart disease. This study showed that waking BP surge (defined using arising time precisely identified by actigraphy) positively correlated with left ventricular mass index (LVMI), assessed by echocardiography, in elderly

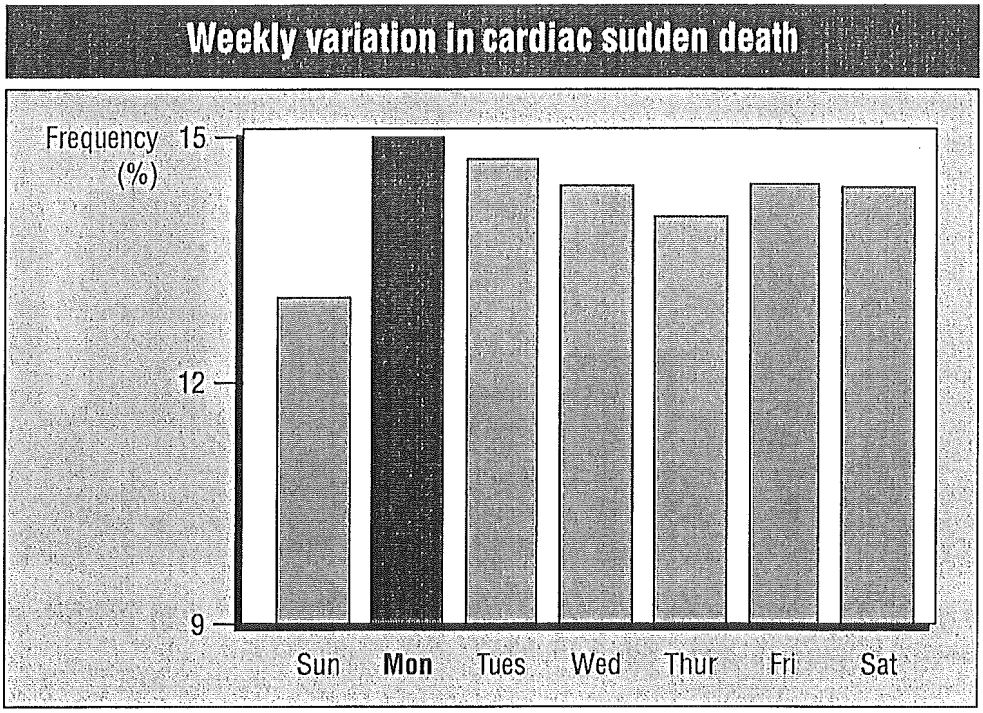

Figure 2.6. *Population-based Berlin Medical System data (24,061 consecutive cases). Reproduced with permission from* Eur Heart J *2000; **21**:315–320.*

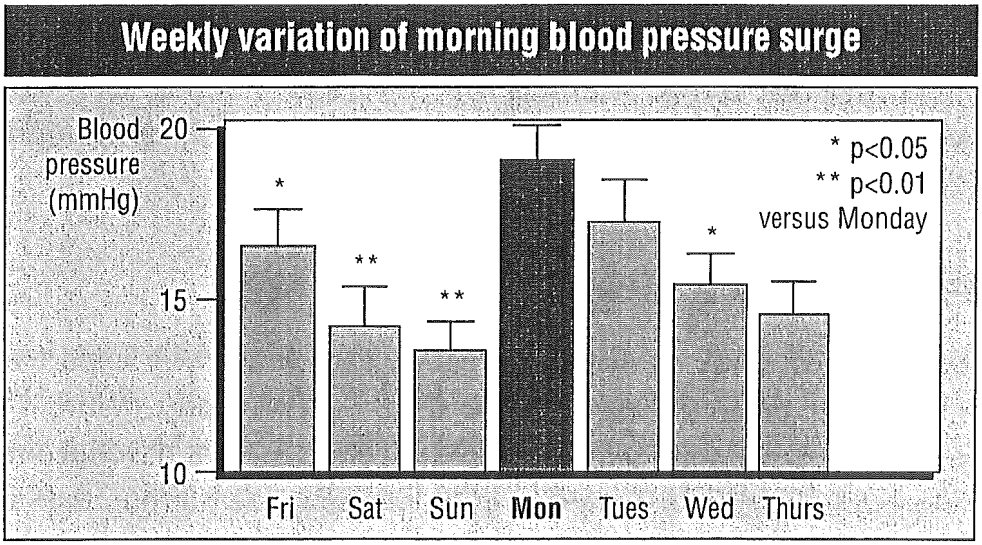

Figure 2.7. *Data from 135 community-dwelling subjects. Reproduced with permission from* Am J Hypertens *2004, in press.*

hypertensive patients [48], as was found in the French prospective study (*see* Figures 2.4 and 2.5) [45].

In addition, hypertensive patients with morning BP surge had prolonged Q–T interval corrected for heart rate (QTc) duration and QTc dispersion compared with those without morning BP surge (*see* Figure 2.8) [49]. These QTc abnormalities found in the morning BP surge groups were only significant in the morning period. Spectral analysis of heart rate variability showed that the low frequency power:high frequency power ratio, an indirect index of sympathetic activity, was significantly higher in the morning BP surge group than in the nonsurge group. Thus, in the surge groups, increased sympathetic activity in the morning leads to prolonged QTc dispersion. As this increased QTc dispersion is reported to be associated with LVH and cardiac arrhythmia, exaggerated morning BP surge also appears to be associated with increased risk for cardiac arrhythmia and sudden death in the morning in hypertensive patients.

Complications in diabetes

In a cross-sectional study in newly-diagnosed type 2 diabetic normotensive patients, morning BP levels and morning BP surge were significantly increased in patients with microalbuminuria compared with patients without microalbuminuria, despite this, there was no significant difference in the daytime BP and nighttime BP between the two groups (*see* Figure 2.9) [50].

In another study on type 2 diabetic patients, those with morning BP hypertension (morning BP level measured at home >130/85 mmHg) had marked frequencies of diabetic renal disease, retinopathy, microvascular disease and vascular complications, including coronary artery disease and cerebrovascular disease (*see* Figure 2.10). In this study, hypertension defined by clinic BP level was not associated with these complications [51].

In the recent study on asymptomatic hypertensive patients with and without type 2 diabetes, silent cerebral infarcts were evaluated by brain MRI. Hypertensive patients were classified into four groups and the risk of multiple silent cerebral infarcts was comparable between diabetic patients with white-coat hypertension (WCHT) and nondiabetic patients with sustained hypertension (*see* Figure 2.11) [52]. The patients with both diabetes

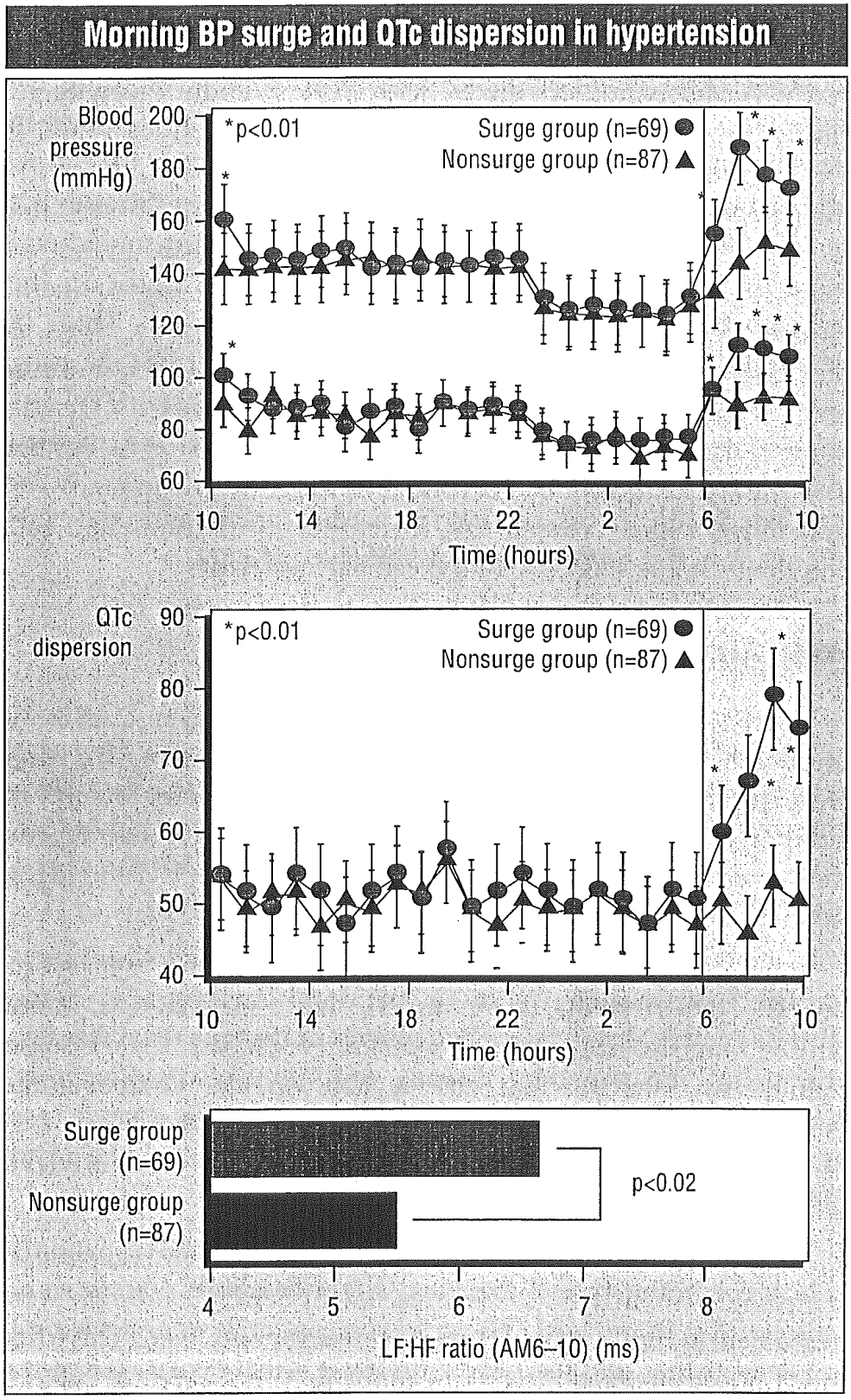

Figure 2.8. *BP, blood pressure; QTc, Q–T interval corrected for heart rate; LF:HF, low frequency:high frequency. Reproduced with permission from* Hypertension *2003;* ***41****:237–243.*

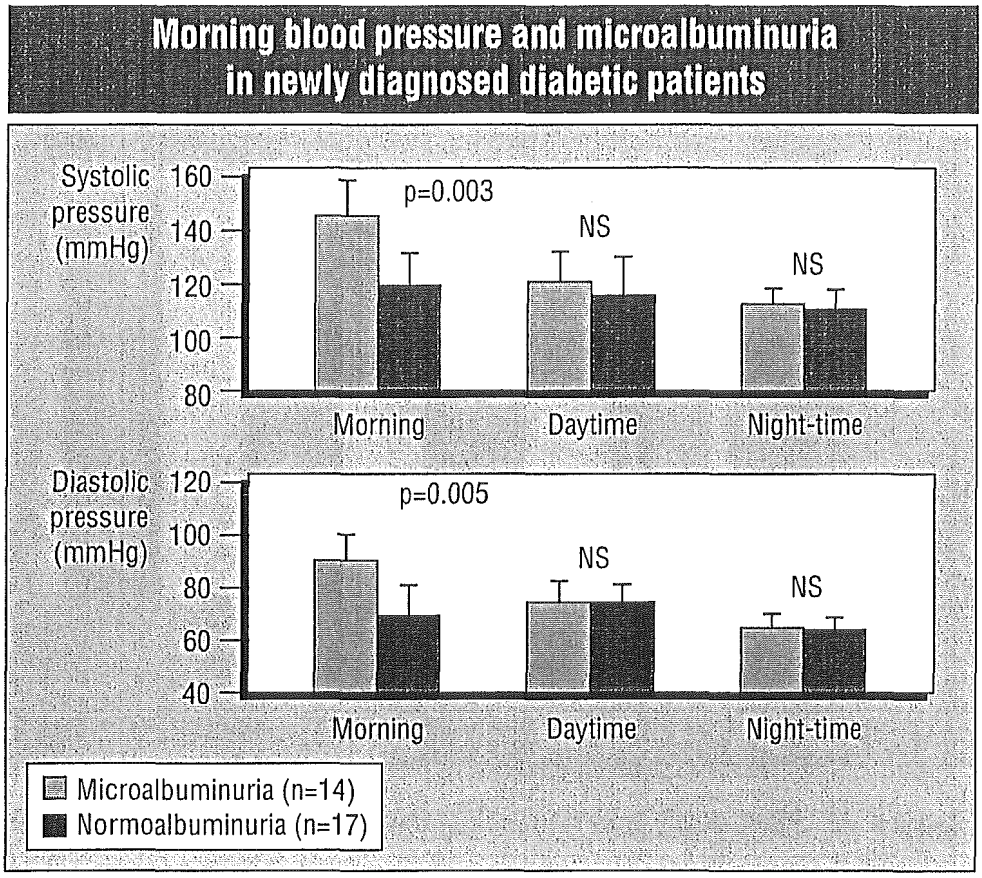

Figure 2.9. *NS, not significant. Reproduced with permission from* N Engl J Med *2003;* ***348****:260–264.*

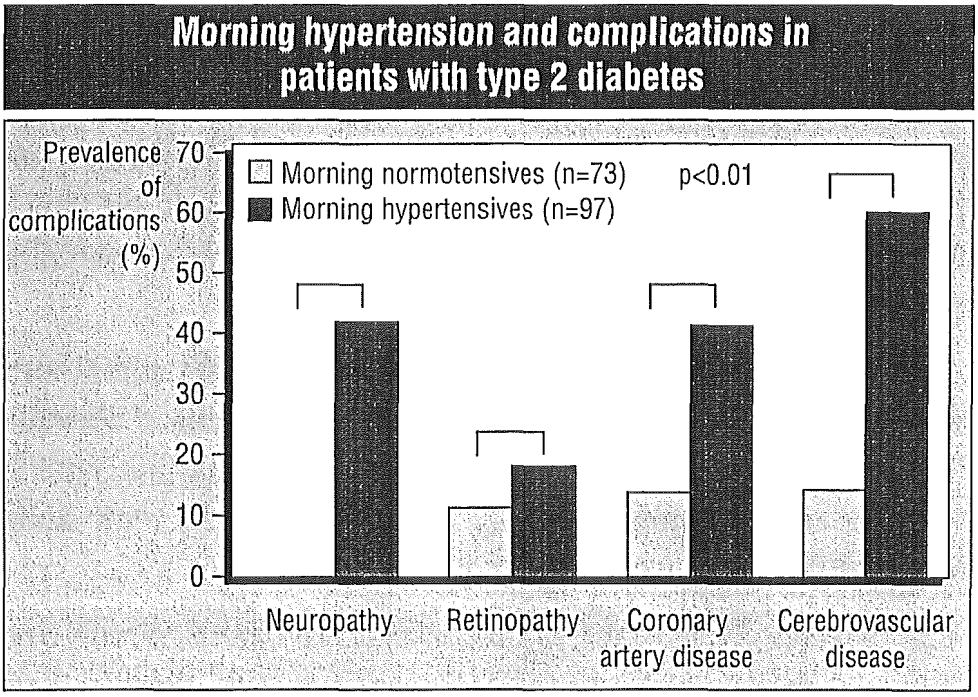

Figure 2.10. *Reproduced with permission from* Diabetes Care *2002;* ***25****:2218–2223.*

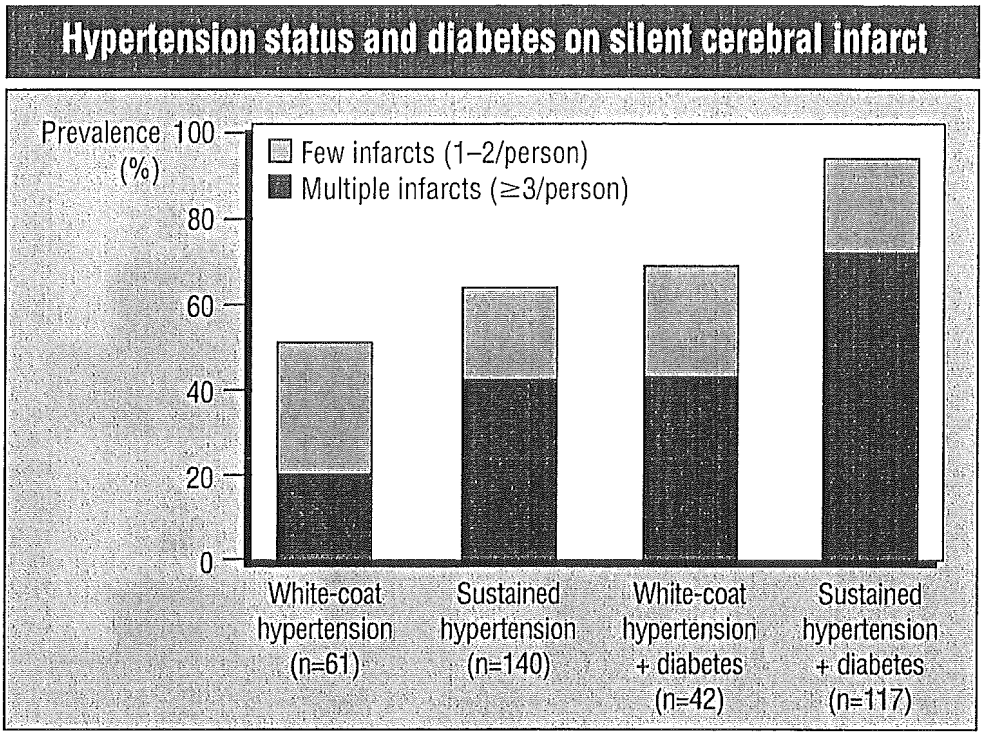

Figure 2.11. *Reproduced with permission from* Stroke *2003; 4:2471–2474.*

and sustained hypertension had the highest risk for multiple silent cerebral infarcts. Cardiac remodelling is also advanced in hypertensive patients with diabetes; in hypertensive patients, the presence of diabetes increased relative wall thickness (*see* Figure 2.12) [53]. Concentric hypertrophy, which is the worst prognosis, was more frequently found in hypertensive patients with diabetes.

Patients with diabetes, particularly those with autonomic nervous system dysfunction, are also likely to have a nondipping pattern of nocturnal falls in BP. This nondipping pattern precedes microalbuminuria [54] and is associated with poor prognosis [55].

As diabetes is one of the worst conventional cardiovascular risk factors, target BP levels are lower for patients with diabetes than than those without diabetes. Night-time and morning BP levels should be monitored more closely in patients with diabetes.

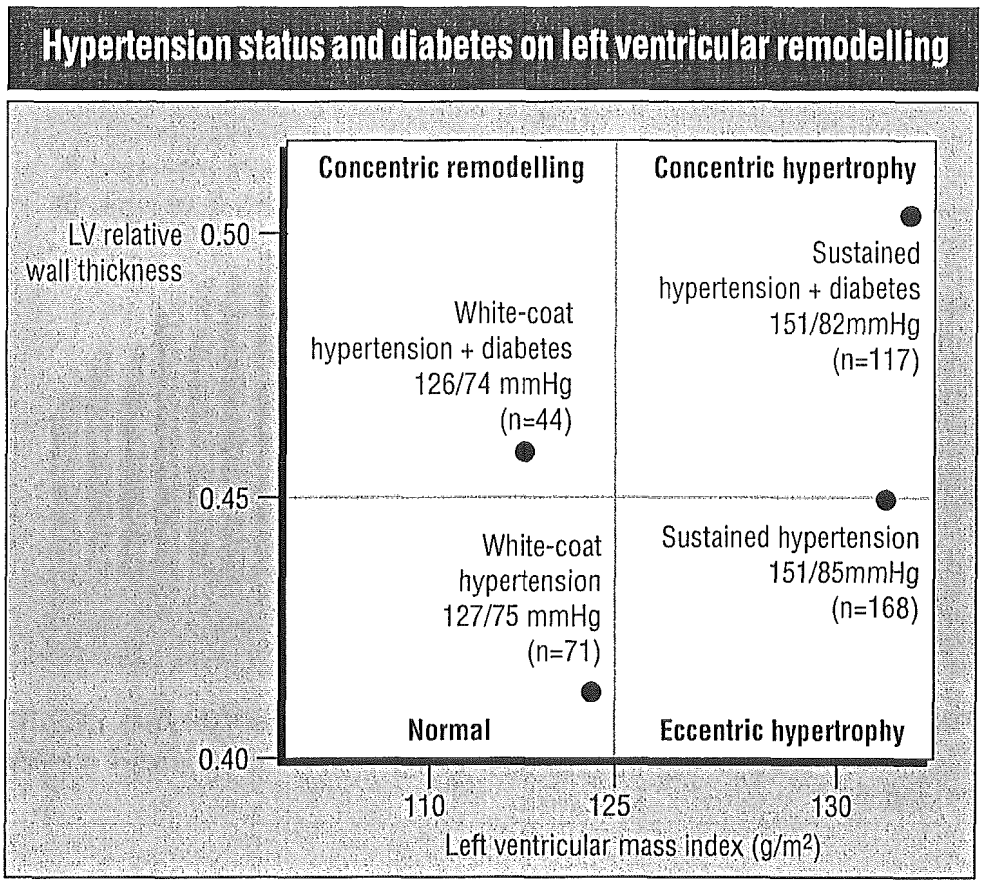

Figure 2.12. *LV, left ventricle. Reproduced with permission from* Am J Hypertens *2004; in press.*

Augmented risk of morning blood pressure surge

The risk of target organ damage and cardiovascular events due to morning BP surge may be augmented in patients with impaired autoregulation of blood vessels of target organs. In these patients, morning surge in systemic BP may lead directly to morning pressure surge in target organs. Patients with diabetes, even if they are normotensive, are likely to have impaired autoregulation; morning surge in systemic BP in these patients, again, may lead directly to morning surge in intraglomerular pressure causing a deterioration in renal function. Elderly patients also tend to have impaired autoregulation of target organ vessels and morning peak was enhanced in elderly patients when compared with younger adults (*see* Figure 2.13) [46].