(HALT), bedtime administration of alpha$_1$-blocker, doxazosin, predominantly reduced morning BP [93,94]. In another study in hypertensive patients [57], morning BP and morning BP surge was shown to be reduced by bedtime dosing of doxazosin, when compared with ambulatory BP over other periods (*see* Figure 5.3) [57]. In addition, the alpha-adrenergic morning BP surge was defined as the reduction of morning BP surge by doxazosin. The alpha-adrenergic morning BP surge was closely associated with multiple silent cerebral infarcts (10 mmHg increase: odds ratio [OR]=1.96, p=0.006), independent of age, morning BP surge, 24-hour SBP and other cofactors. Figure 5.4 shows the scatter plots of morning BP surge and alpha-adrenergic morning BP surge, indicating that the slope of the regression lines was significantly different between those patients with multiple silent cerebral infarcts and those without [57]. This result indicates that morning BP surge, particularly that which is dependent on alpha-adrenergic

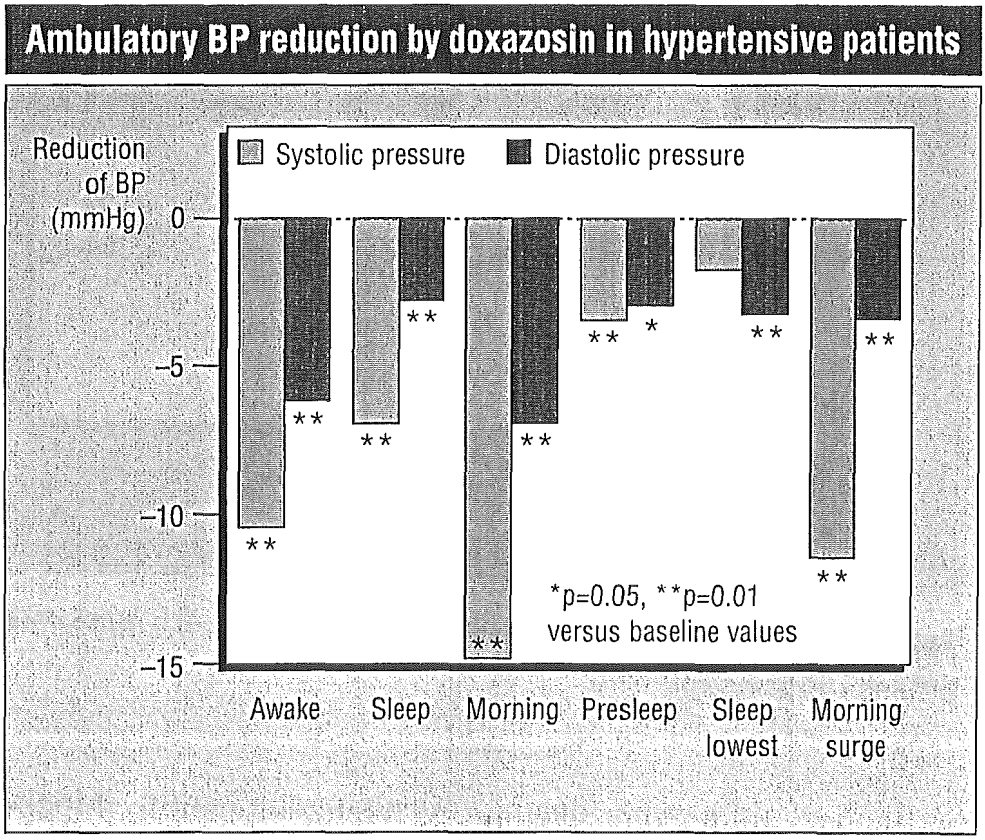

Figure 5.3. *BP, blood pressure. Reproduced with permission from* Am J Hypertens *2004; **17**:668–675.*

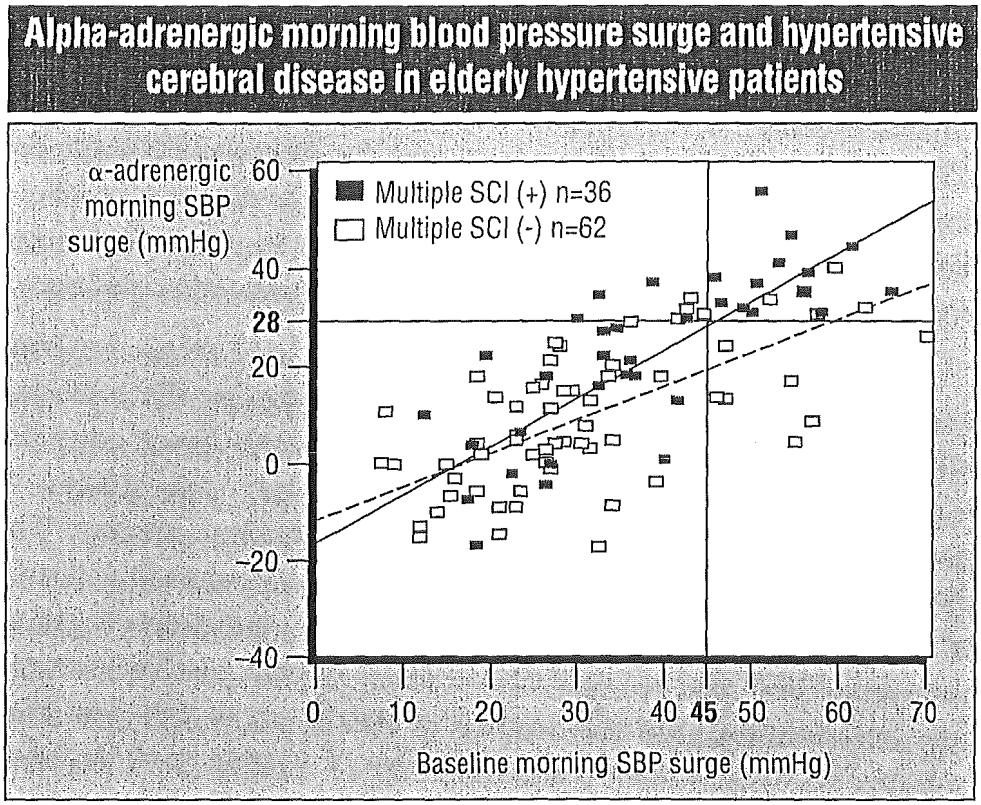

Figure 5.4. *SBP, systolic blood pressure; SCI, silent cerebral infarcts (detected by brain magnetic resonance imaging). Reproduced with permission from* Am J Hypertens *2004; **17**:668–675.*

activity, is closely associated with advanced silent hypertensive cerebrovascular disease in elderly patients.

There is no evidence that beta-adrenergic blockers reduce morning BP surge specifically, however, theoretically, they are effective for morning hypertensive patients with morning surge in heart rate. The effectiveness of beta-adrenergic blockers on cardioprotection is well validated.

Angiotensin-converting enzyme inhibitors

The RAAS is activated in the morning and could contribute to morning BP surge and morning increase in cardiovascular risk. Long-acting angiotensin-converting enzyme (ACE) inhibitors have been reported to lower the ambulatory BP without disruption of the diurnal BP variation.

Recently, it has been demonstrated that, in addition to circulating factors in the cardiovascular system, the tissue RAAS also exhibits diurnal variation, possibly in relation to a clock gene [12,67,95]. In addition to the reduction of the morning BP level, the morning activation of the tissue RAAS could be suppressed effectively, leading to increased protection against hypertensive target organ damage and cardiovascular events in hypertensive patients.

Trandolapril is an ACE inhibitor with the one of the longest-acting ACE inhibitory activity profiles and, therefore, BP lowering effect due to its lipophilic nature [96]. Specifically timed administration of trandolapril, just before going to bed, may achieve a greater reduction of morning BP in hypertensive patients. The effects on morning BP of bedtime dosing versus morning dosing of trandolapril were studied. In the bedtime-administered group, prewaking SBP (the average of two hours of SBP just before waking) and morning SBP (the average of two hours of SBP just after waking) were significantly decreased by 11 mmHg (p=0.005) and 8.4 mmHg (p=0.03), respectively (*see* Figure 5.5). On the other hand, in the morning-administered group, the reduction of prewaking SBP (3.9 mmHg) and morning systolic BP (6.6 mmHg) did not reach statistical significance. The degree of reduction in 24-hour BP level was comparable between the two groups and there was no additional reduction of the night-time lowest BP in either administration group. Thus, bedtime administration of trandolapril appears to control morning BP in hypertensive patients without causing excessive nocturnal falls in BP.

In the Heart Outcomes Prevention Evaluation (HOPE) trial [97], the ACE inhibitor ramipril significantly reduced cardiovascular morbidity and mortality in patients at high risk for cardiovascular events. The benefit could only partly be attributed to the modest mean reduction of clinic BP during the study period. However, even after adjustment for the changes in SBP (2.4 mmHg) and diastolic BP (1.0 mmHg), ramipril still lowered the risk of the combined primary outcome by 25%, partly indicating a BP lowering effect beyond that of inhibition of RAAS. Another interpretation of this benefit could be the complete control of morning BP, as according to the HOPE protocol, ramipril was given once daily at bedtime and BP was measured during the day.

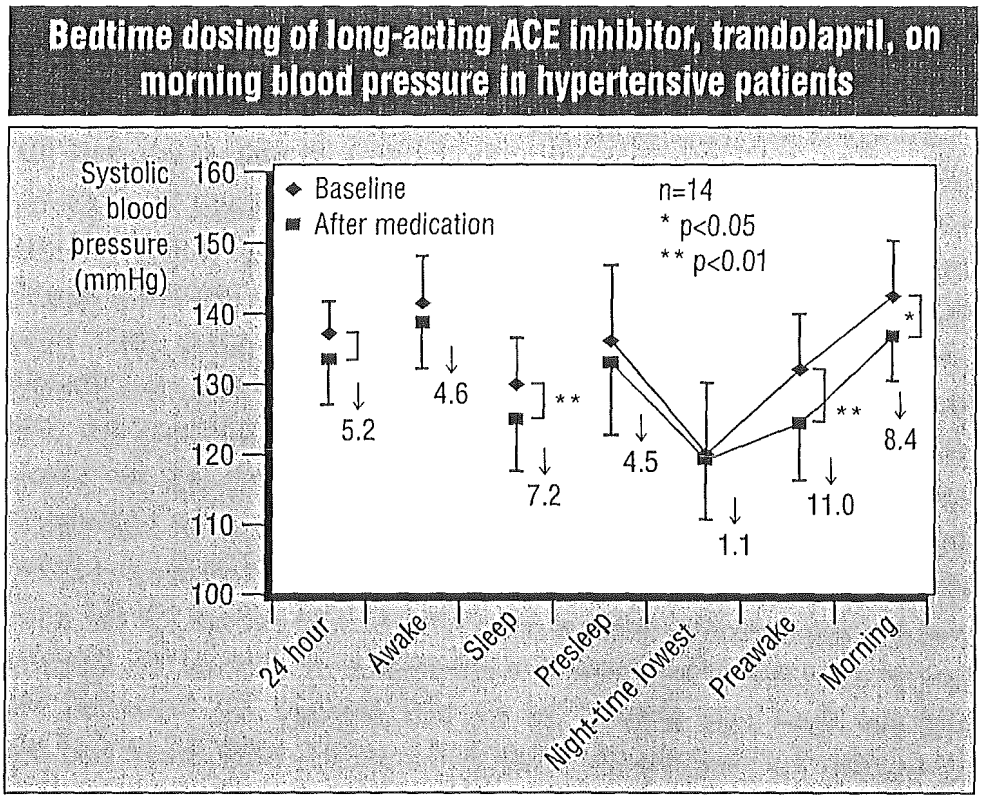

Figure 5.5. *ACE, angiotensin converting enzyme.*

In fact, in the HOPE substudy assessing 24-hour BP using ABPM, a greater BP lowering effect was found during sleep BP than clinic and awake BP [98].

Angiotensin-receptor blockers

As well as ACE inhibitors, recent large clinical trials such as the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), the Study of Cognition and Prognosis in Elderly patients (SCOPE) and the Candesartan in Heart Failure – Assessment of Mortality and Morbidity (CHARM) have confirmed that angiotensin-receptor blockers (ARBs) are effective for target organ protection and for prevention of cardiovascular events [99–101].

In the recent Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, there was no significant difference in cardiac morbidity and mortality between the group that received the ARB valsartan and those on the long-acting calcium antagonist

amlodipine during the overall follow-up period of 4.2 years [102]. However, during the first three months of the study, the primary endpoints of stroke and all-cause mortality were much more frequent in the valsartan group than in the amlodipine group. The differences between the groups were greater than would be expected from the small difference in clinic BP. During the first three months, the differences in BP were 4.0/2.1 mmHg after one month, 4.3/2.5 mmHg after two months and 3.0/2.0 mmHg after three months. The differences in event rates may be due to insufficient lowering of 24-hour ambulatory BP, particularly morning BP, with valsartan. In another recent randomized study [90], the BP lowering effects of valsartan and amlodipine monotherapy on ambulatory BP in 76 hypertensive patients were compared. The drug regimen was the same as that used in the VALUE trial except for the addition of diuretics. Each drug was administered once in the morning and the dose was titrated up to 160 mg/day for valsartan and 10 mg/day for amlodipine. After 8–16 weeks, both drugs had significantly reduced 24-hour BP, although the reduction was significantly smaller in the valsartan group than the amlodipine group. However, the reduction of morning BP was only significant in the amlodipine group (*see* Figure 5.2). The between-group difference in morning SBP was 11 mmHg. These findings might explain the different results in the early cardiac and stroke events noted in the VALUE trial [103].

However, different ARBs have markedly different effects on morning BP levels and morning BP surge. The BP lowering effect of ARBs on morning BP levels and morning BP surge is dependent on differences in plasma half-life and the characteristics of binding to and dissociation from the vascular angiotensin-II receptor [104]. Figure 5.6 shows the plasma half-life differences between each ARB; different results from the VALUE trial may be obtained if other ARBs were used.

Candesartan has a similar elimination half-life, however, its tissue-based half-life and affinity appear stronger than valsartan. A prospective crossover study was performed in 73 essential hypertensive patients to compare the effects of candesartan and lisinopril on ambulatory BP and early-morning BP [105]. Twenty-four-hour ABPM was performed at baseline and for each active treatment.

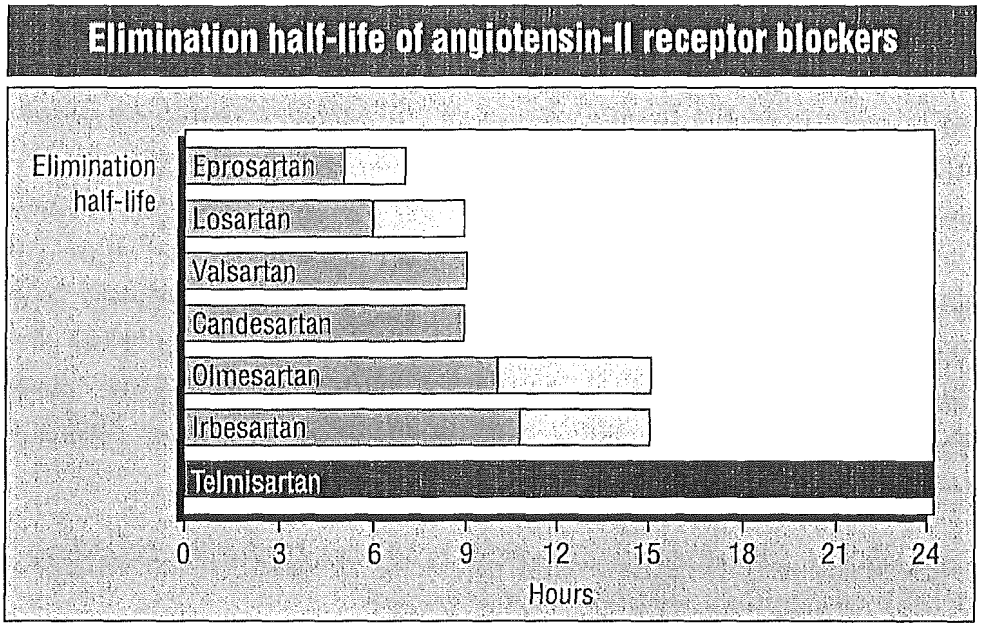

Figure 5.6. *Modified with permission from* Lancet *2000;* ***355****:637–645 and* J Hum Hypertens *2002;* ***16****(Suppl 2):S13–S16.*

Small doses of thiazide diuretic were added as needed. The effects of both drugs on 24-hour BP were almost identical and satisfactory. Patients were classified into a morning surge group (the highest quartile of morning SBP surge >36 mmHg) and a nonmorning surge group (the remaining three quartiles of morning BP surge); candesartan was superior in decreasing morning BP and morning BP surge.

Telmisartan versus other antihypertensive drugs on morning blood pressure

Telmisartan is the ARB with the longest half-life (24 hours) and a meta-analysis of the clinical efficacy has demonstrated superior BP reductions in the morning hours.

One double-blind, randomized trial compared the effect of telmisartan (40–80 mg once daily), which has the longest plasma half-life, with valsartan (80–160 mg once daily), which has an intermediate half-life (6–9 hours), on early morning BP in 490 patients with hypertension [106]. Ambulatory BP recordings were performed at baseline after a placebo period and again after six and

eight weeks of double-blind therapy in a randomized cross-over design. After the active dose, telmisartan reduced the BP during the last six hours of the dosing period by –11(±0.8)/–7.6(±0.6) mmHg compared with –8.7(±0.8)/–5.8(±/0.6) mmHg for patients on valsartan (p=0.02 for SBP and p=0.01 for diastolic BP) (*see* Figure 5.7), indicating that telmisartan achieved a greater effect than valsartan on BP during the early morning period in patients with hypertension. In addition to the above study, as shown in Table 5.1, there is also evidence that telmisartan reduces morning BP levels more effectively than other antihypertensive drugs in different classes, as well as other ARBs.

Peroxisome proliferator-activated receptor-gamma-activating profile of angiotensin-receptor blockers

ARBs have also been shown to reduce the incidence of type 2 diabetes mellitus. A specific subset of ARBs, including telmisartan and irbesartan, activate peroxisome proliferator-activated receptor-gamma (PPAR-γ), a central regulator of insulin and glucose metabolism providing a potential mechanism for their insulin-sensitising

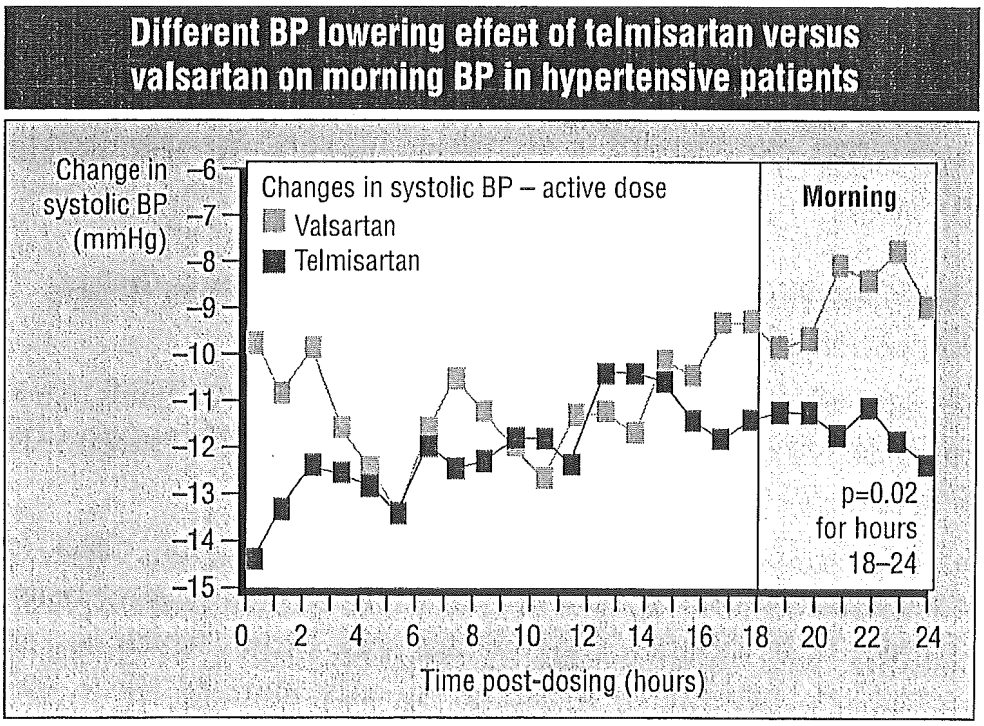

Figure 5.7. *BP, blood pressure. Reproduced with permission from* Am J Hypertens *2004;* ***17****:347–353.*

Morning BP lowering effects of telmisartan versus other antihypertensive drugs in patients with mild to moderate hypertension

Other drugs	Study subjects (n) telmisartan/ others	Evaluated hours	Mean dose (mg/day) telmisartan/others	BP difference (mmHg) telmisartan–other Systolic BP	Diastolic BP	Measurement	Reference
Angiotensin-receptor blocker							
Losartan	360/360	last 6h	40–80/50–100	–2.1(*)	–1.5(**)	Ambulatory BPM	[107]
Losartan + HCTZ	(Tel + HCTZ) 199/198	last 6h	40+HCTZ 12.5/ 50+HCTZ 12.5	–2.5(*)	–1.8(*)	Ambulatory BPM	[108]
	318/320			–2.6(*)	–1.9(*)		[109]
	(Tel + HCTZ) 200/198		80+HCTZ 12.5/ 50+HCTZ 12.5	–3.4(*)	–2.5(***)		[108]
	167/320			–3.4(*)	–2.8(*)		[109]
Valsartan	244/246	last 6h	80/160	–2.3(*)	–1.8(*)	Ambulatory BPM	[106]
Valsartan	468/462	last 6h	80/160	–2.0(**)	–1.8(**)	Ambulatory BPM	[110]
Calcium channel blocker							
Amlodipine	73/78	last 4h	40–120/5–10	–3.9	–3.4(*)	Ambulatory BPM	[111]
Angiotensin-converting enzyme inhibitor							
Perindopril	220/221	Trough	40–80/4–8	–3.4(**)	–1.4(*)	Home BPM	[112]
Ramipril	405/407	last 6h	80/10	–4.7(***)	–3.4(***)	Ambulatory BPM	[113]
Ramipril	397/404	last 6h	80/10	–3.7(***)	–2.7(***)	Ambulatory BPM	[114]

Table 5.1. **p<0.05; **p<0.01; ***p<0.001. BP, blood pressure BPM, blood pressure monitoring; HCTZ, hydrochlorothiazide.*

and antidiabetic effects [115,116]. Eprosartan and losartan do not have this beneficial effect.

Telmisartan has been shown to activate PPAR-γ in humans at normal therapeutic concentrations, whereas irbesartan only activates PPAR-γ at supratherapeutic doses. Olmesartan, candesartan and valsartan have not been shown to have this effect. Some preliminary clinical evidence also demonstrates that telmisartan improves insulin sensitivity [117]. A 12-month, randomized double-blind study on hypertensive patients with diabetes actually demonstrated that telmisartan has some beneficial metabolic effects on lipid profiles when compared with nifedipine gastrointestinal therapeutic system [118]. This favourable metabolic effect of telmisartan was also shown to be significantly superior to eprosartan [119].

Morning hypertension is more closely associated with diabetic complications than clinic hypertension and the American Diabetes Association recommends a lower target BP level of 130/80 mmHg for diabetic hypertensive patients. Strict control of morning hypertension, using ARBs that induce PPAR-γ activity, is recommended for diabetic patients and those with metabolic syndrome.

6

Ongoing clinical trials of angiotensin-receptor blockers

Program of Research tO show Telmisartan End-organ proteCTIOn poteNtial (PROTECTION)

The objective of the Program of Research tO show Telmisartan End-organ proteCTIOn poteNtial (PROTECTION) study is to evaluate the protective effects of telmisartan on target organs in patients at high risk of renal, cardiac and vascular damage [120]. An extensive series of clinical trials is being conducted to compare telmisartan with valsartan, losartan, amlodipine and ramipril in high-risk hypertensive patients. The PROTECTION programme consists of a series of clinical studies that will examine the effects of telmisartan in approximately 6500 hypertensive patients with isolated systolic hypertension, type 2 diabetes, obesity or renal disease. All of the studies will be conducted using state-of-the-art technology, including ABPM. This programme will also investigate the effects of an ARB on key surrogate markers of organ tissue damage. The series of trials will also help to clarify the protective effects of telmisartan in hypertensive patient populations at high risk of clinical events.

Japan Morning Surge – Telmisartan versus Valsartan Comparison Study

The Japan Morning Surge – Telmisartan versus Valsartan Comparison Study will compare telmisartan and valsartan and evaluate the difference in their BP lowering effect on morning BP, insulin resistance and target organ damage (LVH) in Japanese hypertensive patients. There are significant racial differences in the demographics of cardiovascular disease: coronary artery disease is much less common in Japanese people than in Westerners, however, stroke is more common. The higher incidence of stroke in the Japanese population may be partly explained by the popularity of a high-salt diet [37]. This could augment the differences in the effectiveness of different ARBs on morning BP [121].

ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized AssessmeNt Study in aCE iNtolerant subjects with cardiovascular Disease (TRANSCEND)

These large ongoing clinical trials are studying the role of ARBs when used alone or in combination with ACE inhibitors in high-risk populations with controlled hypertension [122]. The primary objectives of the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) are to determine if the combination of the ARB telmisartan and the ACE inhibitor ramipril is more effective than ramipril alone and if telmisartan is at least as effective as ramipril. The Telmisartan Randomized AssessmeNt Study in aCE iNtolerant subjects with cardiovascular Disease (TRANSCEND) will determine if telmisartan is superior to placebo in patients who are intolerant of ACE inhibitors. The primary outcome for both trials is the composite of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure. High-risk patients with coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage are being recruited and followed for 3.5–5.5 years in two parallel, randomized, double-blind clinical trials. Recruitment from 730 centres in 40 countries for ONTARGET (n=25,620) was completed in July 2003 and for TRANSCEND, 5776 patients (out of a projected total of 6000) have been recruited (May, 2004).

Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS) study

The world's largest secondary stroke prevention trial, the Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS) study, is now ongoing. This is a randomized, controlled, double-blind study featuring an innovative 2 x 2 factorial design (telmisartan versus placebo; extended-release dipyridamole plus acetyl salicylic acid versus clopidogrel). The study will attempt to clarify whether telmisartan, in addition to standard stroke prevention therapy, can further reduce the risk of recurrent stroke in 15,500 patients from 600 centres and 27 countries worldwide, during 2003–2007 [123].

7

Summary

Morning hypertension is a serious risk for target organ damage and subsequent cardiovascular events. Even in well-controlled hypertensive patients, taking standard antihypertensive medication, morning hypertension is masked in 50% or more patients. The detection of morning hypertension by home BP monitoring or ABPM and the strict home BP-guided antihypertensive treatment, specifically targeting morning hypertension, would achieve more effective prevention of cardiovascular events in hypertensive patients.

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