

Relevance of blood pressure variation in the circadian onset of cardiovascular events

Thomas Giles

Ambulatory blood pressure monitoring enables the recording of the circadian rhythm of blood pressure under everyday circumstances, with the majority of individuals displaying diurnal variations in both systolic and diastolic blood pressures. During sleep, blood pressure in most people is between 10% and 20% lower than the mean daytime value. On arousal and the start of day-to-day activities, there is a surge in blood pressure that may last for between 4 and 6 h. Extensive evidence shows that ambulatory blood pressure is superior to office values in predicting cardiovascular risk. Cardiovascular events, such as myocardial infarction, ischaemia and stroke are more frequent in the morning hours, soon after waking, than at other times of day. Circadian variations in biochemical and physiological parameters help to explain the link between acute cardiovascular events and the early morning blood pressure surge. Recent observations in elderly Japanese individuals demonstrate that greater early morning blood pressure surges are related to an increased incidence of overt cerebrovascular disease; individuals with the greatest increases in blood pressure on awakening also had the greatest prevalence of silent ischaemic events and were

more likely to experience multiple infarcts. Antihypertensive drugs that provide blood pressure control at the time of the early morning surge should provide greater protection against target-organ damage and enhance patient prognosis. Ambulatory blood pressure monitoring may be particularly helpful in assessing the circadian pharmacodynamics of such antihypertensive drugs. The technique has demonstrated, for example, a significantly greater reduction in blood pressure for the last 6 h of the 24-h dosing interval with telmisartan compared with valsartan. *J Hypertens* 23 (suppl 1):S35–S39 © 2005 Lippincott Williams & Wilkins.

Journal of Hypertension 2005, 23 (suppl 1):S35–S39

Keywords: circadian rhythm, cardiovascular risk, stroke, ambulatory blood pressure monitoring, telmisartan, valsartan

Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA.

Correspondence and requests for reprints to Professor Thomas Giles, Louisiana State University Health Sciences Center, Cardiology, Room 331E, 1542 Tulane Avenue, New Orleans, LA 70112, USA.

Tel: +1 504 568 7861; fax: +1 504 599 1336; e-mail: tgiles@lsuhsc.edu

Introduction

Blood pressure is a continuous variable and usually displays a biorhythm in both normotensive and hypertensive individuals [1]. Typically, blood pressure is highest in the mid-morning and lowest during the night, with a 10–20% difference between mean night-time and mean daytime values [2]. Several haemodynamic, neurohumoral and other factors interact to produce this circadian variation in blood pressure [3]. In addition to diurnal changes in blood pressure, heart rate, total peripheral resistance and, hence, cardiac output vary at different times of the day [4]. Circadian variations in the density of β -adrenoceptors [5] and mRNA expression of angiotensin type 1 receptors [6] have also been detected in animal models.

The renin–angiotensin–aldosterone system (RAAS) is activated in the early morning before arousal, with increased production of renin [7] and angiotensin II [8], as a result of activation of the sympathetic nervous system [3]. In the healthy individual, this is a physiological adjustment to compensate for the change from a horizontal to a vertical position and consequent increased cardiovascular demand [9]. This is reinforced by the

observation that night-shift workers have an inversed circadian rhythm, with a peak blood pressure at 23.00 h [10]. However, if the RAAS is dysregulated, the large increases in angiotensin II concentrations of the order of 200% that occur in the early morning may have serious pathological consequences. In addition to vasoconstriction, angiotensin II brings about vascular inflammation and increased risk of thrombosis via effects on the coagulation and thrombolytic systems [11].

There is now considerable circumstantial evidence for a link between the morning surge in blood pressure and increased cardiovascular risk. Acute cardiovascular events display a similar circadian pattern, with increased vulnerability during the early morning hours; this article reviews the evidence. In the development of drugs that modulate the pathophysiological changes mediated by the RAAS, the effects of such agents on the circadian rhythm of blood pressure and their impact on cardiovascular disease are important considerations.

Importance of ambulatory blood pressure

The original research into the circadian variation in blood pressure was performed by intra-arterial recordings [1].

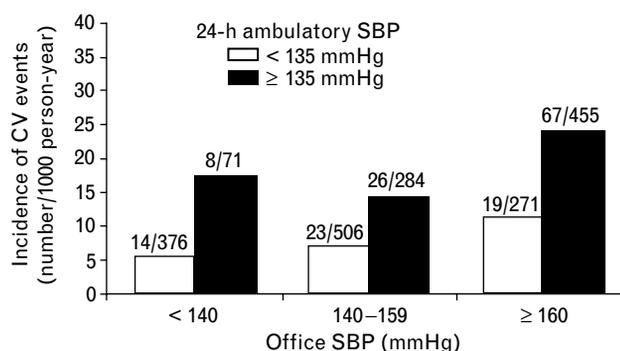
Table 1 Prospective studies showing the predictive value of ambulatory blood pressure is superior to office blood pressure

Authors	Year	Population	n	Comments
Perloff <i>et al.</i> [20]	1983	Referred	1076	Low risk if ambulatory blood pressure < office blood pressure
Verdecchia <i>et al.</i> [21]	1994	Referred	1187	White-coat hypertension patients at low risk
Imai <i>et al.</i> [22]	1996	Population	1789	Ambulatory and home blood pressure predictive, office blood pressure not
Redon <i>et al.</i> [23]	1998	Refractory	86	Low risk if ambulatory blood pressure < office blood pressure
Khattar <i>et al.</i> [24]	1998	Referred	479	White-coat patients at low risk (intra-arterial recording)
Staessen <i>et al.</i> [25]	1999	Syst-Eur trial	808	Ambulatory blood pressure gives better prediction
Clement <i>et al.</i> [26]	2003	Treated hypertensive patients	1963	Raised ambulatory blood pressure predictive

Syst-Eur, Systolic Hypertension in Europe.

The development of compact, non-invasive ambulatory blood pressure monitors has facilitated the recording of the circadian rhythm of blood pressure in individuals under everyday circumstances, with the minimum of inconvenience to the individual. The use of ambulatory blood pressure monitoring (ABPM) has expanded in recent years, with increasing use in day-to-day clinical practice. The technique provides a picture of the 24-h haemodynamic load and is valuable in the prediction of outcome in patients with treated or untreated hypertension. There is extensive evidence that overall target-organ damage score [12], left ventricular mass [13], impaired left ventricular function [13,14], albuminuria [15–17], brain damage [18] and microvascular disease, in particular retinopathy [19], correlate better with 24-h mean blood pressure than with office blood pressure. This does not, however, invalidate the usefulness of routine office blood pressure measurements in monitoring the progress of patients with high blood pressure and the effectiveness of antihypertensive therapy.

The predictive value of ambulatory blood pressure measurement, and its superiority to office blood pressure measurements, has been demonstrated in prospective studies (Table 1) [20–26]. The most recent of these (Office versus Ambulatory blood pressure; OvA) is the first to be performed in patients receiving treatment for hypertension [26]; Clement and co-workers enrolled 1963 hypertensive patients and followed them for approximately 5 years. Over this period, new cardiovascular events were identified in 157 patients. Among patients in three categories of office systolic blood pressure (SBP; <140 mmHg, 140–150 mmHg and \geq 160 mmHg), a 24-h mean ambulatory SBP \geq 135 mmHg predicted a greater incidence of cardiovascular events than did a 24-h mean ambulatory SBP < 135 mmHg (Fig. 1). After adjustment for age, sex, smoking status, diabetes, serum cholesterol

Fig. 1

Higher ambulatory systolic blood pressure (SBP; \geq 135 mmHg) in hypertensive patients predicts cardiovascular (CV) risk. (Reproduced from Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, *et al.* Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003; **348**:2407–2415 [26], with permission. Copyright © 2003 Massachusetts Medical Society. All rights reserved.)

concentrations, body mass index, treatment with lipid-decreasing drugs, history of cardiovascular events and office blood pressure, it was found that greater mean 24-h ambulatory SBP and diastolic blood pressure (DBP) were independent risk factors for a new cardiovascular event.

One of the important uses of ABPM is in the identification of individuals with white-coat hypertension, defined as a normal ambulatory blood pressure (24-h mean <120/80 mmHg) despite increased office values (>140/90 mmHg). This is a relatively frequent phenomenon, being present in 20–35% of so-called ‘hypertensive individuals’ [27]. Fagard *et al.* [28], in the Systolic hypertension in Europe (Syst-Eur) trial, did not find evidence that such patients benefit from antihypertensive treatment, as there was no difference in outcome compared with that obtained with placebo. The importance of this finding is reflected in the relatively recent introduction of Medicare coverage for ABPM in order to evaluate patients with white-coat hypertension.

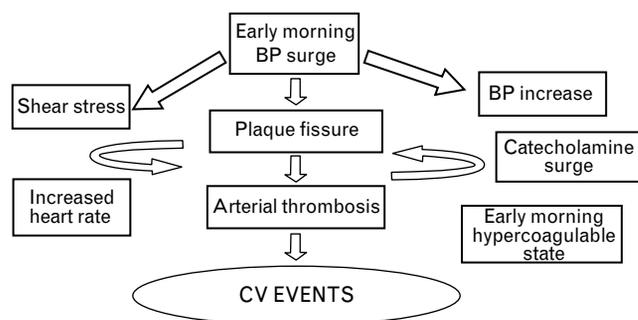
The converse situation can also occur: white-coat normotension (otherwise known as ‘masked hypertension’), in which office blood pressure is within the normal range, but the ambulatory blood pressure is elevated [29]. The phenomenon has not been extensively studied, as sufferers are not easily identified. In individuals with an awake mean ambulatory SBP/DBP of > 134/90 mmHg and an office blood pressure of < 140/90 mmHg, Liu and colleagues [30] found that the thicknesses of the left ventricles and the carotid wall were similar to those in patients with sustained hypertension; this was despite average differences in office blood pressure of 25/16 mmHg.

Triggering of cardiovascular events

The relationship between the early morning blood pressure surge, which may last for between 4 and 6 h [31], and cardiovascular events is not fully understood. Haemodynamic, haematological and neurohumoral factors may all be contributory (Fig. 2). Many cardiovascular events are precipitated by fissure of atherosclerotic plaques and consequent arterial thrombosis [32]. Before rupture, these lipid-rich plaques are not obstructive, but have a thin fibrous covering that is susceptible to fissure in response to increasing shear stress associated with the surge in blood pressure. The situation is amplified by increased sympathetic activity and plasma catecholamine concentrations [33], with a consequent increase in heart rate (Fig. 3) [34]. Other contributory factors are increases in vascular tone [35], platelet aggregability [36,37] and blood viscosity [38], together with decreases in protective factors, including fibrinolytic and vagal activity [39].

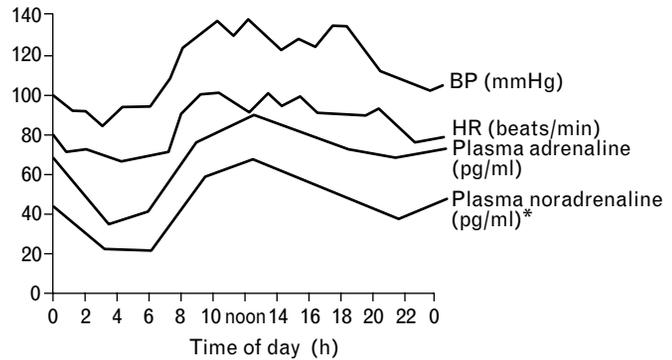
The clinical consequences of these haemodynamic and neurohumoral changes are numerous. A significant circadian surge in transient myocardial ischaemia on awaking has been detected, for example, in patients with coronary artery disease [40]. Peak ischaemic activity, measured by the Holter ST-segment depression, has been observed in the first and second hours after awakening. This finding provides an explanation as to why many patients report that they experience angina more frequently, or even exclusively, in the morning on arising. Similarly, observations of 1167 patients with ischaemic stroke revealed that the onset of stroke was more common between 10.00 h and 12.00 h than for any other 2-h interval of the day or early evening [41]. It was also found that the late evening was the period when the onset of stroke was least likely [41]. The increased relative risk of an acute myocardial infarction occurring between 06.00 h and 12.00 h, based on the proportion of actual numerical incidence compared with the expected number of incidences if no circadian variation existed, has been calculated by Cohen and co-workers [42], using data from 66 635 patients in 30

Fig. 2



Mechanisms triggering cardiovascular events during the early morning blood pressure surge. BP, blood pressure; CV, cardiovascular.

Fig. 3



Circadian variations in haemodynamics and plasma catecholamine concentrations. *Noradrenaline concentrations have been reduced by 3.5 times for uniformity of scaling. BP, blood pressure; HR, heart rate.

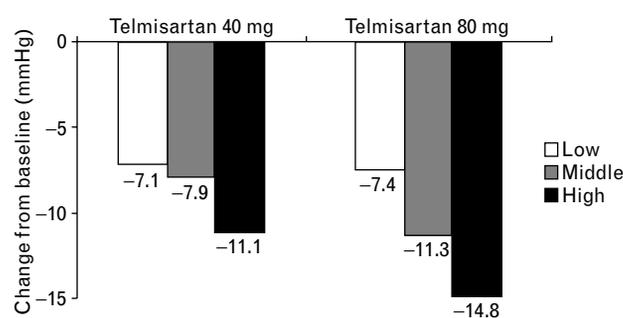
published studies, to be 38%. Furthermore, meta-analysis of data from 31 publications for the onset of 11 816 strokes of all types found that the increased relative risk of occurrence between 06.00 h and 12.00 h was 49% [43].

A recently reported study illustrates the importance of the rate of increase in the haemodynamic load, as a result of dysregulation of the RAAS, for the risk of a cardiovascular event [44]. ABPM was performed in elderly Japanese patients with hypertension to establish the extent of the morning blood pressure surge, which was calculated as the mean SBP during the 2 h after waking minus the mean value during the 1 h that included the lowest blood pressure while sleeping. Magnetic resonance imaging was also performed to determine the presence of silent cerebral infarcts. Kario *et al.* [44] observed that the prevalence of silent cerebral infarcts was highest in the decile with the greatest morning blood pressure surge (≥ 55 mmHg); furthermore, during the follow-up period, the incidence of stroke was highest in these patients.

Evaluation of antihypertensive efficacy using ambulatory blood pressure monitoring

ABPM is a powerful tool in evaluating the pharmacodynamics of antihypertensive treatment [45]. Given the extensive evidence for the increased prevalence of cardiovascular events in the early morning hours, it is important that the treatment controls blood pressure at this time of day. To promote compliance, most antihypertensive drugs are taken once daily, and usually in the morning after the patient has got out of bed; it is, therefore, crucial that these drugs provide 24-h control of blood pressure to cover the risky early morning period. Evidence for the involvement of the RAAS in the morning blood pressure surge also suggests that agents targeting angiotensin II may be particularly beneficial.

Fig. 4



Effects of telmisartan 40 mg (WB White, personal communication) and 80 mg [46] on nocturnal systolic blood pressure, according to baseline values in tertiles of low, middle and high.

By analysing the 24-h ambulatory blood pressure database for telmisartan, White and Larocca [46] have shown that, after 4–8 weeks of treatment with telmisartan at a dose of 80 mg, the mean SBP and DBP were reduced between 23.00 h and 06.00 h. When the patient population was divided into tertiles, it was demonstrated that the change in blood pressure was dependent on the baseline nocturnal blood pressure. The smallest reduction in nocturnal blood pressure was observed in the tertile with lowest baseline nocturnal DBP (75 mmHg), and greatest reduction occurred in the tertile with the highest nocturnal DBP (94 mmHg) (Fig. 4). Similar observations were recorded in patients treated with telmisartan 40 mg (WB White, personal communication).

The recently published randomized, double-blind trial, MICArdis missed DOse study (MICADO) identified the important differences in the antihypertensive efficacies of telmisartan and valsartan at the end of the once-daily dosing interval [47]. The purpose of the study was to determine whether telmisartan, which has a half-life of about 24-h [48], is able to provide superior blood pressure control at the end of the dosing interval compared with valsartan, which has a shorter half-life of about 7–9 h [49]. After a placebo run-in and randomization, both telmisartan and valsartan were given once daily at the lower doses of 40 mg and 80 mg, respectively, for 2 weeks before forced titration to 80 mg and 160 mg, respectively. MICADO demonstrated that, compared with valsartan, telmisartan provided significantly superior reductions in mean SBP ($P = 0.02$) and DBP ($P = 0.01$) 18–24 h after dosing. These observations suggest that the recommended once-daily dosing of valsartan when treating hypertension may provide insufficient cardiovascular protection; indeed, in the Valsartan in Heart Failure Trial (Val-HeFT), for example, trial valsartan was administered twice daily [50].

Conclusions

Enhanced prediction of cardiovascular risk is provided by 24-h ABPM. In day-to-day clinical practice, the technique enables the identification of patients with white-coat hypertension, in whom the risk of a cardiovascular event is relatively low. In patients with evidence of target-organ damage, such as left ventricular hypertrophy, ABPM may identify masked hypertension.

The uses of ABPM extend to the evaluation of the efficacies of antihypertensive drugs. Data from 24-h ABPM may predict protection against target-organ damage, in addition to being used in evaluating the duration of action of drugs, thus establishing frequency of dosing, and determining effects on the circadian rhythm of blood pressure.

References

- 1 Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. *Lancet* 1978; **i**:795–797.
- 2 White WB. Relevance of blood pressure variation in the circadian onset of cardiovascular events. *J Hypertens* 2003; **21**(suppl 6):S9–S15.
- 3 Giles TD. Factors influencing circadian variability. *Blood Press Monit* 2000; **5**(suppl 1):S3–S7.
- 4 Rizzoni D, Agabiti-Rosei E. Relationships of cardiac function and structure to blood pressure rhythms. *Ann N Y Acad Sci* 1996; **783**: 159–171.
- 5 Witte K, Parsa-Parsi R, Vobig M, Lemmer B. Mechanisms of the circadian regulation of beta-adrenoceptor density and adenylyl cyclase activity in cardiac tissue from normotensive and spontaneously hypertensive rats. *J Mol Cell Cardiol* 1995; **27**:1195–1202.
- 6 Naito Y, Tsujino T, Fujioka Y, Ohyanagi M, Iwasaki T. Augmented diurnal variations of the cardiac renin-angiotensin system in hypertensive rats. *Hypertension* 2002; **40**:827–833.
- 7 Portaluppi F, Bagni B, Degli UE, Montanari L, Cavallini R, Trasforini G, et al. Circadian rhythms of atrial natriuretic peptide, renin, aldosterone, cortisol, blood pressure and heart rate in normal and hypertensive subjects. *J Hypertens* 1990; **8**:85–95.
- 8 Kala R, Fyhrquist F, Eisalo A. Diurnal variation of plasma angiotensin II in man. *Scand J Clin Lab Invest* 1973; **31**:363–365.
- 9 Muller JE. Morning increase of onset of myocardial infarction. Implications concerning triggering events. *Cardiology* 1989; **76**:96–104.
- 10 Sternberg H, Rosenthal T, Shamiss A, Green M. Altered circadian rhythm of blood pressure in shift workers. *J Hum Hypertens* 1995; **9**: 349–353.
- 11 Strawn WB, Ferrario CM. Mechanisms linking angiotensin II and atherogenesis. *Curr Opin Lipidol* 2002; **13**:505–512.
- 12 Verdecchia P, Borgioni C, Ciucci A, Gattobigio R, Schillaci G, Sacchi N, et al. Prognostic significance of blood pressure variability in essential hypertension. *Blood Press Monit* 1996; **1**:3–11.
- 13 White WB, Lund-Johansen P, Omvik P. Twenty-four-hour blood pressure load as a surrogate end-point in assessing antihypertensive therapy. *J Hypertens* 1993; **11**(suppl 1):S75–S80.
- 14 Mancia G, Zanchetti A, Agabiti-Rosei E, Benemio G, De Cesaris R, Fogari R, et al. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. *Circulation* 1997; **95**:1464–1470.
- 15 Giaconci S, Levanti C, Fommei E, Innocenti F, Seghieri G, Palla L, et al. Microalbuminuria and casual and ambulatory blood pressure monitoring in normotensives and in patients with borderline and mild essential hypertension. *Am J Hypertens* 1989; **2**:259–261.
- 16 Hansen KW, Christensen CK, Andersen PH, Pedersen MM, Christiansen JS, Mogensen CE. Ambulatory blood pressure in microalbuminuric type 1 diabetic patients. *Kidney Int* 1992; **41**:847–854.
- 17 Opsahl JA, Abraham PA, Halstenon CE, Keane WF. Correlation of office and ambulatory blood pressure measurements with urinary albumin and N-acetyl-beta-D-glucosaminidase excretions in essential hypertension. *Am J Hypertens* 1988; **1**:117–120.
- 18 Shimada K, Kawamoto A, Matsubayashi K, Ozawa T. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. *Hypertension* 1990; **16**:692–699.

- 19 Poulsen PL, Bek T, Ebbelohj E, Hansen KW, Mogensen CE. 24-h ambulatory blood pressure and retinopathy in normoalbuminuric IDDM patients. *Diabetologia* 1998; **41**:105–110.
- 20 Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressure. *JAMA* 1983; **249**:2793–2798.
- 21 Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994; **24**:793–801.
- 22 Imai Y, Ohkubo T, Sakuma M, Tsuji I, Satoh H, Nagai K, et al. Predictive power of screening blood pressure, ambulatory blood pressure and blood pressure measured at home for overall and cardiovascular mortality: a prospective observation in a cohort from Ohasama, northern Japan. *Blood Press Monit* 1996; **1**:251–254.
- 23 Redon J, Campos C, Narciso ML, Rodicio JL, Pascual JM, Ruilope LM. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension* 1998; **31**:712–718.
- 24 Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10-year follow-up study. *Circulation* 1998; **98**:1892–1897.
- 25 Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999; **282**:539–546.
- 26 Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003; **348**:2407–2415.
- 27 White WB. Ambulatory blood-pressure monitoring in clinical practice. *N Engl J Med* 2003; **348**:2377–2378.
- 28 Fagard RH, Staessen JA, Thijs L, Gasowski J, Bulpitt CJ, Clement D, et al. Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. *Circulation* 2000; **102**:1139–1144.
- 29 Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension* 2002; **40**:795–796.
- 30 Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Ann Intern Med* 1999; **131**:564–572.
- 31 Weber MA. The 24-hour blood pressure pattern: does it have implications for morbidity and mortality? *Am J Cardiol* 2002; **89**(suppl 2A):27A–33A.
- 32 Fuster V, Steele PM, Chesebro JH. Role of platelets and thrombosis in coronary atherosclerotic disease and sudden death. *J Am Coll Cardiol* 1985; **5**(suppl 6):175B–184B.
- 33 Turton MB, Deegan T. Circadian variations of plasma catecholamine, cortisol and immunoreactive insulin concentrations in supine subjects. *Clin Chim Acta* 1974; **55**:389–397.
- 34 Linsell CR, Lightman SL, Mullen PE, Brown MJ, Causon RC. Circadian variations of epinephrine and norepinephrine in man. *J Clin Endocrinol Metab* 1985; **60**:1210–1215.
- 35 Panza JA, Epstein SE, Quyyumi AA. Circadian variation in vascular tone and its relation to alpha-sympathetic vasoconstrictor activity. *N Engl J Med* 1991; **325**:986–990.
- 36 Jovicic A, Ivanisevic V, Nikolajevic R. Circadian variations of platelet aggregability and fibrinolytic activity in patients with ischemic stroke. *Thromb Res* 1991; **64**:487–491.
- 37 Jovicic A, Mandic S. Circadian variations of platelet aggregability and fibrinolytic activity in healthy subjects. *Thromb Res* 1991; **62**:65–74.
- 38 Talan MI, Engel BT. Morning increase in whole blood viscosity: a consequence of a homeostatic nocturnal haemodynamic pattern. *Acta Physiol Scand* 1993; **147**:179–183.
- 39 Feng DL, Toffler GH. Diurnal physiologic processes and circadian variation of acute myocardial infarction. *J Cardiovasc Risk* 1995; **2**:494–498.
- 40 Rocco MB, Barry J, Campbell S, Nabel E, Cook EF, Goldman L, et al. Circadian variation of transient myocardial ischemia in patients with coronary artery disease. *Circulation* 1987; **75**:395–400.
- 41 Marler JR, Price TR, Clark GL, Muller JE, Robertson T, Mohr JP, et al. Morning increase in onset of ischemic stroke. *Stroke* 1989; **20**:473–476.
- 42 Cohen MC. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. *Am J Cardiol* 1997; **79**:1512–1516.
- 43 Elliott WJ. Circadian variation in the timing of stroke onset – a meta-analysis. *Stroke* 1998; **29**:992–996.
- 44 Kario K, Pickering TG, Umeda Y, Hoshida S, Hoshida Y, Morinari M, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation* 2003; **107**:1401–1406.
- 45 Palatini P. Importance of various methods of blood pressure measurement in clinical trials. *Curr Hypertens Rep* 2000; **2**:362–369.
- 46 White WB, Larocca GM. Improving the utility of the nocturnal hypertension definition by using absolute sleep blood pressure rather than the "dipping" proportion. *Am J Cardiol* 2003; **92**:1439–1441.
- 47 White WB, Lacourcière Y, Davidai G. Effects of the angiotensin II receptor blockers telmisartan versus valsartan on the circadian variation of blood pressure: impact on the early morning period. *Am J Hypertens* 2004; **17**:347–353.
- 48 Neutel JM, Smith DHG. Dose response and antihypertensive efficacy of the AT₁ receptor antagonist telmisartan in patients with mild to moderate hypertension. *Adv Ther* 1998; **15**:206–217.
- 49 Markham A, Goa KL. Valsartan. A review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997; **54**:299–311.
- 50 Cohn JN, Tognoni G, Glazer RD, Spormann D, Hester A. Rationale and design of the Valsartan Heart Failure Trial: a large multinational trial to assess the effects of valsartan, an angiotensin-receptor blocker, on morbidity and mortality in chronic congestive heart failure. *J Card Fail* 1999; **5**:155–160.