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Blood Pressure Control and Primary Prevention of Stroke: Summary of the Recent Clinical Trial Data and Meta-Analyses

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Abstract Stroke is the second most common cause of death worldwide and of adult disability, but in the near future the global burden of cerebrovascular diseases will rise due to ageing and adverse lifestyle changes in populations worldwide. The risk of stroke increases at blood pressure levels above 115/75 mm Hg and high blood pressure (BP) is the most important modifiable risk factor for stroke, associated with 54 % episodes of stroke worldwide. There is strong evidence from clinical trials that antihypertensive therapy reduces substantially the risk of any type of stroke, as well as stroke-related death and disability. The risk attributed to BP is associated not only with absolute values but also with certain parameters describing BP diurnal pattern as well as short-term and long-term variability. Many studies reported that certain features of BP like nocturnal hypertension, morning surge or increased variability predict an increased stroke risk. However, there is no accepted effective modality for correction of these disturbances (chronotherapy, certain classes of antihypertensive drugs). In the elderly, who are mostly affected by stroke, the primary prevention guidelines recommend treatment with diuretics and calcium channel blockers to lower blood pressure to the standard level.

Keywords Stroke · Risk, risk factors · Blood, blood pressure · Ambulatory, ambulatory blood pressure measurement · Circadian, circadian rhythm · Non, non-dipping · Morning, morning surge · Blood, blood pressure variability · Antihypertensive, antihypertensive treatment · Randomized, randomized clinical trial · Meta, meta-analysis · Hypertension

Search strategy We searched using the electronic databases MEDLINE (1966–August 2013), EMBASE and SCOPUS (1965–August 2013). The main data search terms were: blood pressure, stroke, hypertension, intensive (aggressive) hypotensive therapy, morning surge, white coat, blood pressure variability, nondipping, therapy and treatment.

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Introduction

For last three decades, stroke remains the second most common cause of mortality [1] and recently has become the third leading cause of global disease burden estimated using disability-adjusted life years [2]. In developed countries, despite decreased incidence of stroke, paradoxically the absolute number of stroke victims still raises because of rapid ageing of population and tight correlation of stroke risk with age [3]. These trends are accompanied by a decline of the mean age of stroke victims, which is now 69 years [4]. On the contrary, in low income and middle income countries the incidence of stroke is growing and nowadays two-thirds of all individuals that have suffered from a stroke live in developing countries where stroke is the second cause of disabilities. Due to these trends in global health, cerebrovascular disease is predicted to remain the second leading cause of mortality, reaching almost eight million annual deaths by 2030 [5] .

Blood Pressure and the Risk of Stroke

The relationship between hypertension and stroke was first described by Frederick Akbar Mohamad - a physician of mixed Indian and Irish origin working in Guy's Hospital in London in the 19th century. He constructed a quantitative sphygmograph to estimate the level of blood pressure and described a natural history of essential hypertension, including initial asymptomatic stage, subclinical lesions (left ventricular hypertrophy) and finally, clinical complications, including cerebrovascular accidents like transient ischemic attacks

("a passing paralysis") or stroke ("severe apopleptic seizure") [6].

In the 20th century, major risk factors for stroke were identified and their relative impact estimated. Globally, 51 % of stroke deaths are attributable to high systolic BP and local rates of incidence of stroke are correlated with the prevalence of hypertension. Hypertension is the major modifiable factor and the second most powerful risk factor after age, regardless of geographic location and ethnic background. Blood pressure is a major determinant of both ischemic and hemorrhagic stroke (intracerebral and subarachnoid) and correlates with the risk of the first as well as recurrent episodes of cerebrovascular incidents.

Components of Blood Pressure and the Risk of Stroke

The Framingham Heart Study is the longest-running, prospective epidemiologic project, initiated in 1948 to identify potential and reversible causes of cardiovascular diseases. Although originally the study was designed to analyze causes of coronary heart disease in men younger than 60 years, after six decades of research it provided valuable information on the effects of different factors on the risk of stroke and cognitive dysfunction.

Results of the first cohort of subjects showed that hypertensive patients (with BP>160/95 mm Hg) had the incidence of stroke five to more than 30 times higher as compared to normotensive persons (<140/90 mm Hg) depending on age and gender. The increased risk was also noted in so-called "borderline hypertensives". Using data [7] from subjects aged 55-84 years and free of cerebrovascular disease at the time of data collection, probability of stroke was calculated. The Framingham stroke prediction algorithm (http://www.framinghamheartstudy.org/risk/stroke.html) included SBP values and age, diabetes mellitus, smoking, history of cardiovascular disease, presence of atrial fibrillation, left ventricular hypertrophy and the use of hypertensive medication.

Initial observations from the Framingham study found casual SBP as good as a predictor of stroke as various components of BP, including diastolic and mean arterial pressure, pulse pressure, as well as lability of pressure [8].

Individual data of 958,074 subjects participating in 61 separate prospective studies without known cardiovascular disease at the baseline were used in the meta-analysis [9] to calculate correlation between BP and mortality from stroke. This is the largest meta-analysis ever published, which was preceded by earlier studies by the same group of authors including smaller groups of subjects [10, 11]. The results of Prospective Study Collaboration show that in patients between 40-89 years of age, BP is strongly and directly associated with total vascular and stroke mortality. Each difference of 20 mm Hg of systolic and 10 mm of diastolic Hg was associated with doubling the risk of stroke death. This correlation was continuous without any evidence of a threshold down to at least 115/75 mm Hg. For stroke mortality, average BP was a slightly better predictor than any components of BP, and systolic BP was more informative than diastolic BP or pulse pressure (SBP-DBP difference). The pattern of correlation between BP and stroke mortality was similar in males and females, any type of stroke and geographical regions.

Results of the meta-analysis by the Prospective Study Collaboration are contradictory to some previous findings, which identified a widened pulse pressure as an independent marker of cardiovascular risk, including stroke [12]. For example, analysis of data from the elderly with isolated systolic hypertension from SHEP (Systolic Hypertension in the Elderly Program) study demonstrated an 11 % increase in stroke risk and a 16 % increase in risk of all-cause mortality for each 10-mm Hg increase in pulse pressure [13]. Since widened pulse pressure results from increased conduit vessel stiffness, this association may indicate more advanced lesions in arteries and other target organs. These findings were confirmed by meta-analysis of three trials including systolic hypertension in the elderly (European Working Party on High Blood Pressure in the Elderly, Systolic Hypertension in Europe Trial (Syst-Eur), and Systolic Hypertension in China Trial (Syst-China) [14].

Similarly, in a Finnish study of 4,333 men and 5,270 women aged 45-64 years with no history of vascular disease, the risk of coronary heart disease, stroke, cardiovascular disease and all-cause mortality increased with the increasing pulse pressure during 15 years of follow up, independent of the DBP level. However, after adjustment for systolic blood pressure, the positive association between mortality and increasing pulse pressure disappeared [15].

Results of some studies suggest that an ethnic background may modify the impact of BP on stroke risk. The Reason for Geographic And Racial Differences in Stroke (REGARDS) study included 30,239 black and white individuals over 45 years of age, who were observed for at least 4.5 years. Among white participants, a difference in SBP of 10 mm Hg was associated with an 8 % increase in stroke risk; among black participants, a 10-mm Hg difference was associated with a 24 % increase. The black-white disparity was higher in younger individuals and at a higher SBP level. The results of the REGARDS study suggest that blacks are more susceptible to stroke but the difference may be also attributed to higher prevalence and poorer control of high BP in Afro-Americans [16].

In eastern Asian countries, stroke was a leading cause of death with a greater incidence, higher mortality and greater proportion of hemorrhagic stroke as compared to Western Europe and North America. The Eastern Stroke and

Coronary Heart Disease Collaboration Project aimed to study associations of diastolic BP and cholesterol level with the cardiovascular risk in populations in China and Japan. Using data from 124,774 participants the authors suggested a stronger impact of DBP on stroke risk than in Western countries [11] . However, they have not confirmed their own data in the following Prospective Study Collaboration using global registry (see above).

The majority of studies included in the Prospective Study Collaboration meta-analysis recorded only stroke-related mortality, not incidence; also, type of stroke was not identified in about half of the cases. The INTERSTROKE study evaluated risk factors for first-time acute stroke in 22 countries in order to determine major modifiable risk factors [17••]. The data on 3,000 strokes (78 % ischemic) were collected and compared with 3,000 matched control cases. Type of stroke was diagnosed using neuroimaging and hypertension and was defined either as self-reported or when BP higher than 160/90 was measured during examination. Five risk factors were identified that contributed to 80 % of stroke risk: hypertension, smoking status, waist-to-hip ratio, diet and physical activity. Hypertension was diagnosed in 55 % and 83 % of patients with ischemic and hemorrhagic stroke, respectively, while among controls there were 37 % subjects with high BP. Five other risk factors accounted for an additional 10 % of stroke risk: diabetes mellitus, alcohol use, psychosocial factors , cardiac causes and ratio of apolipoprotein B to apolipoprotein A1. Some other factor, not analyzed in the INTERSTROKE study, may affect the risk of cerebrovascular risk. For example, hypertensive patients with a first-ever episode of stroke had a larger left atrial size and left ventricular mass index [18].

The results of the INTERSTROKE study showed that hypertension was the strongest risk factor for all types of stroke, with the greater risk for intracerebral haemorrhagic stroke than for ischaemic stroke. The impact of hypertension was greater in individuals younger than 45 years than in those aged 45 years or older.

Office and Ambulatory Measurements and the Risk of Stroke

Due to multiple readings, ambulatory blood pressure monitoring (ABPM) offers better accuracy of assessment of a subject's BP with higher sensitivity and specificity for diagnosis of hypertension than office-based BP measurements [19]. A number of studies have suggested that the risk of target-organ damage and cardiovascular complications correlates more closely with 24-hour, daytime, or nighttime ABPM than with the office pressure [20]. Moreover, only ABPM allows for detection of abnormalities in circadian rhythm of BP like white-coat or masked hypertension, non-dipping or extreme dipping and morning surge. Results of ABPM readings can be used to calculate variables, like the ambulatory arterial stiffness index that can better estimate target organ lesions and cardiovascular risk [21].

However, prospective studies using ABPM for cardiovascular risk assessment included relatively small groups with a limited number of outcome events, frequently stroke episodes were not reported separately [22]. Conen and Bamberg made a meta-analysis which included 9,299 participants with 11.1 years of follow up [23] and 881 cardiovascular events. They found a consistent association between mean 24-h systolic BP and cardiovascular mortality and morbidity, even after adjustment for office BP. ABPM was a stronger predictor of stroke than other cardiovascular events, such as cardiovascular and total mortality. For each 10 mm Hg increase of 24-h SBP , there was a hazard ratio (95 % confidence interval) of 1.33 (1.22-1.44) for stroke, 1.19 (1.13-1.26) for cardiovascular mortality, 1.12 (1.07-1.17) for total mortality and 1.17 (1.09-1.25) for cardiac endpoints.

In their meta-analysis , daytime and nighttime BP have a similar ability to predict cardiovascular events, including stroke; however, higher nighttime BP was associated with increased total mortality as well as cardiovascular mortality. The results of their meta-analysis are confirmed by recent data from the IDACO study (International database on Ambulatory blood pressure in relation Cardiovascular Outcomes) which shows that 24-h systolic BP was a stronger predictor of stroke than cardiac events and cardiovascular mortality [24].

Unfortunately, there are limited data on 24-h DBP; therefore, the effect of diastolic values on the risk of stroke and other cardiovascular complications cannot be estimated. The Dublin Outcome Study included 5,292 untreated hypertensive patients who had clinic and ambulatory blood pressure measurement at baseline, and they were followed for a median period of 8.4 years [25]. With adjustment for gender, age, body mass index, smoking status, diabetes, history of cardiovascular events and clinic BP, higher mean values of ambulatory blood pressure were independent predictors for cardiovascular mortality. The relative hazard ratio for each 10-mm Hg increase in systolic blood pressure was 1.12 (1.06 to 1.18; $p=0.001$) for daytime and 1.21 (1.15 to 1.27; $p=0.001$) for nighttime systolic blood pressure. The hazard ratios for each 5-mm Hg increase in diastolic blood pressure were 1.02 (0.99 to 1.07; $p=$NS) for daytime and 1.09 (1.04 to 1.13; $p=0.01$) for nighttime diastolic pressures. Nighttime ABPM provided additional predictive information over daytime ABPM, as does ABPM SBP over ABPM DBP, for total, cardiovascular, stroke, and cardiac mortality.

In most of these studies, ABPM was recorded in initially untreated subjects or during a placebo run-in phase. The Office versus Ambulatory Blood Pressure (OvA) Study included 1,963 patients without history of cardiovascular incident who were followed for a median of five years [26]. All subjects had an ABPM recording after at least three

months of blood pressure lowering treatment and a higher ambulatory systolic or diastolic blood pressure predicted for cardiovascular events even after adjustment for classic risk factors including office measurements of blood pressure. For cerebrovascular outcomes analyzed separately, ambulatory blood pressure was not predictive of the risk after adjustment for office blood pressure. However, office SBP was associated with stroke risk, and the number of episodes could be too small (36 patients) to detect a significant association.

Dipping Status and the Risk of Stroke

The average nocturnal BP is approximately 15 percent lower than daytime values in both control and hypertensive patients. Based on 24-hour BP monitoring, subjects can be classified as nondippers (nocturnal reduction of systolic pressure by <10 % of awake systolic pressure), dippers (reduction by ≥10 % to <20 %), and extreme dippers (reduction by ≥20 %). In some patients so-called "reverse dipping" has been described with an increase in BP during nighttime [27•]. The dipper/nondipper classification of nocturnal blood pressure was first introduced in 1988 when a retrospective analysis suggested that hypertensive patients without nocturnal fall in BP had a higher risk of stroke than the majority of patients with a dipping pattern [28]. Dipping pattern is associated not only with clinical cerebrovascular events but also with the development of silent brain infarcts [29]. In asymptomatic hypertensive patients who underwent 24-hour monitoring and brain magnetic resonance imaging, the frequency of asymptomatic cerebrovascular damage (silent infarcts and advanced deep white matter ischemic lesions) was higher in nondippers as compared to dippers, and extreme dippers had more advanced cerebrovascular lesions [30, 31].

Since then, there have been many studies evaluating morbidity and dipping status, and most large-scale prospective studies support the concept that a diminished nocturnal blood pressure decline is associated with a worse prognosis [32, 33]. Moreover, three longitudinal studies conducted in patients with hypertension have shown that a diminished nocturnal decline in blood pressure predicts cardiovascular events [34–36]. One study suggested that daytime pressure is a better predictor of cardiac events than nighttime pressure, the latter being more important for stroke [37].

The first prospective study to demonstrate that a diminished nocturnal decline in blood pressure is a risk factor for cardiovascular mortality, independent of the overall blood pressure load during a 24-hour period, was the Ohasama study in a Japanese population, which showed that, on average, each 5 % decrease in the decline in nocturnal blood pressure was associated with 20 % greater risk of cardiovascular mortality. Importantly, this association was observed not only in hypertensive individuals but also in normotensive individuals [38]. Kario et al. [36] prospectively observed group of 575 patients with sustained hypertension and known dipping status. Baseline brain magnetic resonance imaging (MRI) disclosed that the percentages with multiple silent cerebral infarcts were 53 % in extreme-dippers, 29 % in dippers, 41 % in nondippers, and 49 % in reverse-dippers. During follow up for an average duration of 41 months, they recorded 54 stroke incidents, and there was a J-shaped relationship between dipping status and stroke incidence (extreme-dippers, 12 %; dippers, 6.1 %; nondippers, 7.6 %; and reverse-dippers, 22 %). Intracranial hemorrhage was more common in reverse-dippers (29 % of strokes) than in other subgroups (7.7 % of strokes, $p < 0.04$).

Despite the absolute risk of cardiovascular complications, the relation to blood pressure is lower in women than in men, the relation between differences in ABPM values and the rates of cardiovascular complications – including stroke - is higher. Data published by the IDACO consortium showed a much steeper relation of all cardiovascular events and stroke with nighttime BP. Again, the BP level achieved at night was more important than the amount of dipping per se. In this study 9,357 subjects (4397 women) were prospectively observed for the median of 11.2 years and both office and 24-hour ambulatory BP were recorded [39].

White Coat Hypertension and the Risk of Stroke

In many patients blood pressure taken in the office may be substantially higher than BP during normal daily activities. White coat hypertension (WCH), also called isolated clinic or office hypertension, is diagnosed when BP is elevated in the office at repeated visits but remains normal out of the office, either on ABPM or HBPM. The prevalence of WCH ranges from 10 to more than 20 percent, and appears to be higher in children and the elderly. A white coat hypertension effect may also occur in patients with apparently resistant hypertension and is called "white coat reaction". In a study of nearly 500 treated hypertensive patients (over 60 percent on three or more antihypertensive agents), 37 % had normal BP on ABPM [40].

The prognostic relevance of WCH still remains a matter of controversy. Cross-sectional studies demonstrated a higher frequency of target organ damage in patients with WCH than in normotensive controls [41]. Results of longitudinal studies show that cardiovascular risk was slightly higher compared with persistent normotension but well below the risks associated with either masked or sustained hypertension. In three prospective cohort analyses including nearly 6,000 subjects followed for a median of 7.5 years, the risk of stroke was 15 % greater in WCH patients as compared to normotensive population, but the difference was not statistically significant [42]. Analysis of subjects with WCH among patients with isolated systolic hypertension included in the IDACO

database show no difference in cardiovascular risk between normotensive and WCH patients, either treated or untreated. However, observed risk was significantly higher compared to patients with masked or sustained hypertension. Stroke episodes were not analyzed separately [43]. In a recent meta-analysis which included nearly 8,000 untreated subjects with WCH diagnosed by means of ABPM, there was no significant difference in cardiovascular risk between normotensive and WCH patients [44].

However, a small number of patients included in studies with short time of follow-up and low initial cardiovascular risk make an unequivocal demonstration of correlation between WCH and increased CV risk difficult. Therefore, WCH cannot be considered an innocent finding. In the Hisayama Study 2,915 Japanese aged over 40 years had ABPM performed along with ultrasound screening for carotid atherosclerosis [45]. As compared to normotensive population, subjects with WCH had significantly higher intima-media thickness of the carotid artery (0.73 mm vs. 0.67 mm, $p<0.001$) and increased likelihood of carotid stenosis (odds ratio 2.36 with 95 % CI 1.27-4.37).

In long-term studies, the incidence of stroke in WCH patients began to rise after 6-8 years of observation [42, 44]. Although they have "normal" ABPM or HBPM, still their values are slightly, yet significantly higher, than BP levels recorded in normotensive controls [46]. They also show a greater prevalence and severity of metabolic risk factors and are characterized with a greater 24-hour BP variability [47].

WCH patients are frequently treated, and the reduction of clinic BP leads to a reduced incidence of CV events. In the Hypertension in the Very Elderly Trial [48], treatment of hypertensive subjects over 80 years of age with indapamide/perindopril versus matching placebo was associated with a 30 % reduction in the rate of fatal or nonfatal stroke, a 39 % reduction in the rate of death from stroke as well as lower total mortality and the risk of other analyzed clinical endpoints [48]. In a small group of patients from both active treatment and placebo groups, ABPM was measured and the results suggest that between 40 % and 60 % of eligible participants in the main study may have had WCH [49]. Therefore, in the elderly, WHC may be associated with an increased cardiovascular risk and active treatment could reduce incidence of significant clinical complications, including stroke. To change current clinical practice, appropriate randomized clinical trials should be required.

Masked Hypertension and the Risk of Stroke

The term "masked hypertension" was introduced by Thomas Pickering to describe patients who are normotensive by conventional clinic measurement and hypertensive by ABPM [50]. This phenomenon, also called isolated ambulatory hypertension, has been identified by screening clinical studies, since patients who are normotensive by office readings do not typically undergo ambulatory monitoring. The prevalence of masked hypertension depends on the study population, setting and modality of out-of-office measurement (ABPM or home blood pressure monitoring, HBPM). Meta-analysis which used data from 28 studies including 25,605 subjects found average prevalence of masked hypertension of 16.8 % (95 % CI13.0-20.5 %)[51]. There are two categories of causal mechanism of masked hypertension: selective reduction of office BP relative to out-of-office BP attributed to the "regression to the mean" phenomenon, and the presence of conditions that selectively increase ambulatory BP. These factors may include smoking, increased physical activity, drinking, obesity, anxiety and job stress, male gender and younger age [20, 51–54]. Poor treatment adherence and intake of medications immediately before scheduled visit can also be responsible cause [55].

Patients with masked hypertension have higher left ventricular mass than normotensives [51, 54, 56]. In The Hisayama Study, subjects with masked hypertension had intima-media thickness of the carotid artery similar to sustained hypertensives (0.77 mm) significantly higher than normotensive population (0.67 mm, $p<0.001$), and increased risk of carotid stenosis (odds ratio 1.95 with 95 % CI 1.25-3.03) as compared to control population [45]. These data confirm previous findings from smaller studies [57, 58]. Masked hypertension is associated with an increased pulse wave velocity, a measure of arterial stiffness, similar to sustained hypertensives and significantly higher than in normotensive subjects [58].

Masked hypertension has been associated with an increased long-term risk of sustained hypertension and cardiovascular morbidity similar to stage 1 hypertension. In the latest meta-analysis including eight studies with 7,961 subjects [51], compared with normotension, the overall hazard ratio for cardiovascular events was 2.09 (95 % CI 1.55-2.81) for masked hypertension, 0.96 (95 % CI 0.65-1.42) for WCH and 2.59 (95 % CI 2.9-3.335) for sustained hypertension ($p=0.0001$). All these surveys took into account total cardiovascular complications without separating cerebrovascular events [51, 54, 59].

Because of the risk associated with masked hypertension, ABPM should be considered in patients referred for possible hypertension (for a variety of reasons, such as left ventricular hypertrophy) despite repeatedly normal BP when measured in the clinic [60].

Morning Surge and the Risk of Stroke

Frequency of cardiovascular complications shows a diurnal variation with a peak incidence between 6 AM and noon [61]. Systematic review of the data on timing of the onset of acute

stroke and the subtype of stroke was performed using 31 reports including 11,816 strokes [62]. All cerebrovascular events, ischemic and hemorrhagic stroke as well as transient ischemic episodes, displayed a significant variation in time of onset. The time period of the highest risk was found between 6 and 9 AM and the lowest number of events occurred from midnight to 3 AM. There was a 58 % "morning excess" of strokes when compared with the value expected if all strokes had been evenly distributed. Risk of all subtypes of stroke was increased during morning hours (6 AM to noon): 55 % for ischemic stroke, 34 % for hemorrhagic stroke and 76 % for transient ischemic accidents. Diurnal pattern in stroke onset is independent of patient demographics, clinical features, or predisposing risk factors [63, 64].

Morning excess of cardiovascular risk parallels the normal circadian pattern of BP, heart rate, physical activity, plasma catecholamines, cortisol, and other humoral and nervous factors. Cerebral blood flow, autoregulation and cerebrovascular reactivity to physiologic stimuli are impaired in the morning and that might explain the increased risk of stroke [65]. Also, increase in sympathetic activity, impaired endothelial function and increased platelet aggregability could contribute to morning excess of cardiac and cerebral events [66].

Some studies suggest that circadian system modulates not only cardiovascular risk markers (i.e., BP or heart rate) at rest but also their reactivity to environmental factors [67]. In certain subjects an exaggerated BP response to regular daily physical activity can be observed and for that phenomenon the term "morning surge" was coined.

Kario and associates first demonstrated that this phenomenon is an independent risk factor for cardiovascular diseases, including stroke. This findings were confirmed in six prospective studies (for review see [68••]. Subjects with "morning surge" – even without hypertension, have a higher incidence of target organ damage (left ventricular hypertrophy, carotid atherosclerosis, intima-media thickness, pulse wave velocity), higher levels of inflammatory markers and urinary catecholamines and albumin excretion [69–71].

Increased stiffness of large arteries results in reduced sensitivity of carotid baroreceptors. Thus, they cannot initiate an effective reflex response to suppress BP surge, particularly in the morning. This notion is supported by a correlation of baroreflex response during the Valsalva maneuver with an increase in morning BP [72].

Morning surge is associated with many factors: ageing, glucose intolerance, alcohol intake, psychological and physical stress, and sleep apnea [68••]. Increases in BP after awakening are higher on Mondays and over the winter and this may explain Monday and winter peak of cardiovascular incidents [73, 74].

However, only one study investigated the association between morning surge and the time of onset of acute cerebrovascular event [75]. The Jichi Medical University School of Medicine Japan Morning Surge Ambulatory Blood Pressure Monitoring Study included 519 older hypertensives with silent cerebral infarct detected on brain MRI, and who were followed up prospectively for an average of 41 months. Incidence of stroke episodes in the morning hours was higher in those with morning surge as compared to subjects without an exaggerated rise in BP after being awake. In this study, the morning surge was associated with stroke events independently of 24-hour BP, nocturnal BP dipping status, and baseline prevalence of silent infarct ($P=0.008$). However, Pierdomenico et al., observing 1,191 elderly treated for hypertension (mean follow up 9.1±4.9 years) found that morning surge of systolic BP was not associated with the risk of stroke in a population as a whole. When dippers and nondippers were analyzed separately, in dippers stroke risk was significantly higher in the third tertile (>23 mm Hg of systolic BP) of morning surge (hazard ratio 2.08 95 % CI 1.03-4.23, $p=0.04$). Stroke risk was significantly and similarly higher in dippers with morning surge >23 mm Hg of systolic BP and in nondippers as compared to the group of dippers with morning surge<23 mm Hg of systolic BP [76].

Morning surge is detected based on ABPM measurements and there are some controversies regarding reproducibility of this phenomenon [77, 78], which may be related to the lack of uniform definition. Studies defining morning surge as the BP 2-hour after rising (morning BP) minus the average BP during sleep (sleep BP) provided the most reproducible results.

There are no clinical studies that pharmacological treatment of morning surge results in regression of target organ damage and prevention of cardiovascular complications. Bedtime dosing of antihypertensive medications may reduce morning rise in BP and it was reported in small open-label studies with doxazosine (The Japan Morning Surge Study 1) and candesartan (the Japan-Target Organ Protection Study). Also, reduction in albumin excretion was observed [79, 80]. However, whether prevention of morning surge as well as reversal of nondipping is possible or beneficial is uncertain and this hypothesis should be tested in randomized clinical trials in the future. Unfortunately, the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial, which was designed to compare chronotherapy with standard treatment was stopped prematurely. However, data available showed that controlled-onset extended-release verapamil was not better than standard therapy with beta-blocker and thiazide for preventing coronary heart disease and stroke [81].

Blood Pressure Variability and the Risk of Stroke

Blood pressure variability (BPV) may be divided into short-term variability including changes in BP from beat-to-beat or within 24 hours, midterm-day by day, and long-term

variability related to BP fluctuations between visits, seasons, years and even decades [82]. Physiologically, short-term changes in BP represent an adaptive response of body regulatory systems to internal and external stimuli. Short-term BPV, usually expressed as the average of standard deviation or coefficient of variation of BP readings during different time intervals, is associated with the risk of cardiovascular complications but is a much weaker predictor of future outcomes than the 24-hour ambulatory blood pressure level [83]. Also, BPV derived from home BP measurements was not a stronger predictor of cardiovascular risk than mean systolic BP [84, 85].

Long-term BPV shows only weak correlation with short term fluctuations (assessed with ABPM) and may result from different determinants like seasonal changes due to ambient temperature and daylight hours, errors in BP readings, low patients' compliance and adherence, and behavioral changes related to workdays and weekends [8, 47, 86]. Results from the twin study suggest that some phenotypes of BPV may be genetically determined [87].

Both short or long term BPV has been associated with development, progression and severity of cardiac, vascular and renal organ damage and with an increased risk of cardiovascular events and mortality, independently of basic BP levels (for review see [88••]. For the first time, investigators of the Swedish Trial in Old Patients with Hypertension (STOP) observed that active treatment reduced the risk of stroke more than it could be attributed to the reduction of BP per se [89]. They suggested that therapy with antihypertensive medications might protect against stroke by decreasing variability in BP.

Recently, Rothwell et al. [90] conducted a post hoc analysis of the data of UK Transient Ischemic Attack aspirin trial (UK-TIA), selecting a cohort of patients with at least seven office BP measurements, once every four months. They found substantial BPV within a single subject from one visit to the next, even when antihypertensive regimen was not changed. In the UK-TIA trial, visit-to-visit systolic BPV was a stronger and independent predictor for future stroke than average systolic BP and its value was similar in subjects treated or not treated for hypertension. These findings were confirmed in three cohorts with a history of ischemic stroke or TIA selected from randomized clinical trials (European Stroke Prevention Study, Dutch TIA and Anglo-Scandinavian Cardiac Outcome Trial-Blood Pressure Lowering Arm, ASCOT-BPLA). In the UK-TIA patients, maximum systolic BP predicted stroke independently of average systolic BP. Patients who did not have sustained hypertension but had episodic severe hypertension at one or more visits had a higher risk of stroke as compared to those with persistent hypertension, despite having lower average systolic BP. There was no association between diastolic BP variability and the risk of stroke.

In the ASCOT-BPLA trial, high-risk hypertensive subjects were randomized to the treatment based on amlodipine adding perindopril mg as required or atenolol adding thiazide diuretic. The majority of patients (89 %) had no history of previous stroke or transient ischemic attack. Compared with the atenolol-based regimen, individuals on the amlodipine-based regimen had a lower risk of fatal and non-fatal stroke (hazard ratio 0.77, 95 % CI 0.66-0.89, $p=0.0003$), total cardiovascular events (hazard ratio 0.84, 95 % CI 0.78-0.90, $p<0.0001$), and all-cause mortality (hazard ratio 0.89, 95 % CI 0.81-0.99, $p=0.025$). Visit-to-visit BPV was a strong predictor of both stroke and coronary events, while average systolic BP was a weaker predictor of both [91].

In their study they also analyzed data from 18,530 patients from the ASCOT-BPLA study without a history of cerebrovascular incident including subgroup of 1,905 participants with repeated ABPM [90]. BPV assessed using ABPM, and expressed as the standard deviation of daytime systolic BP, correlated with visit-to-visit office systolic BPV, and both measures predicted independently of daytime average systolic BP, in particular in younger patients and at lower values of mean systolic BP. Visit-to-visit BPV was a stronger predictor for cardiovascular outcomes than variability on ABPM. Visit-to-visit BPV was greater in the atenolol than in the amlodipine group. In the subsequent meta-analysis they analyzed effects of different classes of antihypertensive drugs on BPV variability and the risk of stroke [92••] – see "Optimal selection for antihypertensive drugs for stroke prevention".

The prognostic importance of visit-to-visit BPV was supported by data from the Third National Health and Nutrition Examination Survey [93]. In a cohort representing the USA population, total mortality was 50 % greater in subjects with the highest tertile of BPV. Data on incidents of stroke were not presented. The relationship between visit-to-visit BPV was also observed in subjects without hypertension. Greater BPV was associated with age, female gender, history of myocardial infarction, higher mean systolic BP and pulse pressure, and use of ACE inhibitors. However, in the European Lacidipine Study on Atherosclerosis (ELSA), which included 1,521 hypertensive patients observed for four years, long-term BPV was not related to the risk of cardiovascular complications (separate number of strokes were not listed). On the contrary, subclinical complications as well as cardiovascular outcomes were significantly correlated with the mean clinic or ambulatory SBP [94].

Recently, Hastie et al. [95] published a study which investigated data on the prognostic value of long-term BPV. In a large population of 16,011 treated hypertensive patients with a follow up extending up to 35 years, they found a consistent association between increasing values of long-term and ultra long-term BPV and risks of cardiovascular and non-cardiovascular mortality, independent from average systolic BP. In contrast to previous studies, no significant

relationship was observed between BPV and stroke mortality. However, previous studies that reported strong links between BPV and stroke assessed stroke incidence, for which the authors had no data. Also, in meta-analysis of 14 clinical trials, greater BPV was not related to higher risk of new-onset atrial fibrillation suggesting that other mechanisms might explain the association between variability and stroke risk [96].

In some studies, measures of intra-individual variability on a visit and not on individual visit-to-visit variability were used, however strict correlation between these two measures of BPV was demonstrated [90]. Using data from the UK-TIA Aspirin Trial and the European Carotid Surgery Trial (ECST), Howard and Rothwell show a reproducibility of repeated BPV measurements in subjects with previous cerebrovascular accidents [97]. This finding was also confirmed in the Cohort Study of Medication Adherence among older Adults (CoSMO) which included 772 elderly with treated hypertension [98] and by the data from the Glasgow Blood Pressure Clinic [95] with mostly patients with uncomplicated hypertension.

Episodic hypertension and high visit-to-visit BPV despite good control of mean BP indicates an increased stroke risk.

Optimal Blood Pressure for Prevention of Stroke

Early trials demonstrated that BP-lowering was effective in preventing stroke in subjects with severe hypertension, in later studies these benefits were also shown in patients with mild to moderate hypertension. In the following clinical trials, reduction in stroke was observed in various populations: elderly, subjects with isolated systolic hypertension, different ethnic groups, subjects with diabetes, high cardiovascular risk, history of coronary heart disease or previous cerebrovascular incident [99]. Results of meta-analysis which used data from 147 randomized clinical trials showed that blood pressure reduction of 10 mm Hg systolic and 5 mm Hg diastolic was associated with a 41 % (33 % to 48 %) reduction in stroke for all trials, 46 % (35 – 55 %) in primary prevention trials, 44 % (21 – 44 %) in secondary prevention trials, and 35 % (20 – 47 %) in trials including subjects with a history of coronary heart disease. The reductions in disease events in the trials were similar to those expected from the cohort study [100••].

The risk of stroke increases continuously above BP values of 115/75 mm Hg. In clinical trials average BP on treatment usually did not fall below 130/80 mm Hg, but available data show continuous reduction of stroke risk parallel to attained BP level. Data from clinical trials do not suggest a J-curve phenomenon between BP and the risk of stroke (see "Targeted Blood Pressure and Stroke—J-curve Phenomenon?") but there are only a few clinical trials which investigated cardiovascular outcomes in subjects treated to different BP goals (for review see [101•].

The Action to Control Cardiovascular Risk In Diabetes – Blood Pressure Arm (ACCORD-BP) study investigated the effect of treatment aimed at intensive lowering of SBP to <120 mmHg (compared to standard therapy) on the incidence of cardiovascular events in 4,733 patients with type 2 diabetes [102]. After a year of treatment, the mean SBP was 119.3 mmHg in the group managed intensively and 133.5 mmHg in the group on standard therapy, while the mean DBP values were 64.4 and 70.5 mmHg, respectively. The incidence of stroke was significantly lower in the group receiving intensive treatment (0.32 % vs. 0.53 %; $p=0.01$); a similar relationship was found for nonfatal stroke (0.30 % vs. 0.47 %; $p=0.03$). However, the incidence of adverse complications of treatment (orthostatic hypotension, hyperkalemia, syncope, bradycardia, arrhythmia or renal function impairment) was significantly increased (3.3 % vs. 1.3 %). There was no significant difference in the primary endpoint, comprising nonfatal MI or stroke, or death due to cardiovascular causes (1.87 % per year in the group on intensive treatment compared with 2.09 % of those on standard therapy; $p=0.20$).

In the Studio Italiano Sugli Effetti CARDIOvascolari del Controllo Della Pressione Arteriosa SIStolica (CARDIO-SIS) study subject ($n=1,111$) with initial systolic BP >150 mm Hg and no diabetes, were randomly allocated to strict control of SBP (target value <130 mmHg; $n=558$), or the standard one (target value <140 mmHg; $n=553$). After two years of follow up, in the strict control group as compared to the typical control, there was a significantly lower risk of total cardiovascular events. There was also a difference in number of incidents of stroke and TIA (1·6 % vs 0·7 %, standard and intensive group, respectively), yet due to low numbers of events they did not reach statistical significance [103].

Meta-analysis of 11 published randomized clinical trials with 42,572 participants investigated the risk of stroke in patients who achieved an intensive (<130 mm Hg) or standard (<140 mm Hg) target of systolic BP. Tight BP control appears to provide additional stroke protection but only among patients with risk factors. Subjects with established cardiovascular disease did not benefit from lowering systolic BP<130 mm Hg [104].

Another meta-analysis compared different BP-lowering agents and different BP intervention strategies on stroke risk in a total of 73,913 patients with diabetes randomized in 31 intervention trials [105]. Allocation to more-tight, compared with less-tight, BP control reduced the risk of stroke by 31 % (relative risk (RR) 0.61, 95 % confidence interval (CI) 0.48-0.79], whereas the reduction in the risk of MI was close to statistical significance [odds ratio (OR) 0.87, 95 % CI 0.74-1.02]. In a meta-regression analysis, the risk of stroke decreased by 13 % (95 % CI 5-20, $P=0.002$) for each 5-mmHg reduction in SBP, and by 11.5 % (95 % CI 5-17, $P<0.001$) for each 2-mmHg reduction in DBP. The risk of

MI did not show any association with the extent of BP reduction.

Current European Guidelines [98] recommend lowering of BP below 140/90 mm Hg for all subjects with hypertension with few exceptions like diabetics (diastolic BP below 85 mm Hg) and elderly over 80 years of age (systolic BP between 140- 150 mm Hg). Some data suggest that further lowering of BP close to optimal level (120/80 mm Hg) may offer additional protection against stroke. However, this strategy can be considered only in subjects with uncomplicated hypertension and initial high stroke risk.

Classes of Antihypertensive Drugs and Stroke Prevention

Starting from the 1980s, randomized trials have compared the effects of different blood pressure lowering medication on cardiovascular events. Meta-analysis of these trials did not find any substantial differences between treatment regimens and combined cardiovascular outcomes. Generally, the major benefit, including protection against stroke, was attributed to the treatment regimen offering lower BP level.

However, some data showing that in the case of primary stroke prevention, calcium channel blockers may be more effective than other groups of drugs. In the ASCOT-BPLA study, a treatment regimen based on amlodipine was more effective in stroke reduction than treatment based on atenolol. However, there was a slightly lower blood pressure achieved in the amlodipine arm than in the atenolol arm, and it may be responsible for observed differences in stroke risk [91]. The reduced risk of stroke in patients treated with a calcium channel antagonist as compared with other classes of BP lowering medications did not reach statistical significance in other trials [100••].

Results of the ASCOT-BPLA trial opened a debate on the role of beta-blockers in the treatment of uncomplicated hypertension. Some group of experts recommended avoiding use of beta-blockers as first line treatment due to their lower protection against stroke [106]. Meta-analysis by Law et al. [100••] included all identified randomized trials of BP lowering drugs in which coronary events or stroke were recorded. The relative risk estimates for stroke in the drug comparison trials were close to 1.0, with two exceptions: greater preventive effect of calcium channel blockers than other drugs (relative risk 0.91, 95 % confidence interval 0.84 - 0.98; $p=0.01$), and a lesser effect of β blockers (relative risk 1.18, 1.03 - 1.36; $p=0.02$). The differences remained significant after adjustment for the small difference in blood pressure reduction between the groups. The observed lesser effect of β blockers, however, was based on trials that directly compared calcium channel blockers with β blockers. Exclusion of the results of these trials from meta-analysis weakened the evidence favoring a disadvantage of β blockers over the three other classes (relative risk 1.11, 0.86 - 1.44; $p=0.40$) but had little effect on the strength of evidence favoring an advantage of calcium channel blockers over the three other classes of drug (relative risk 0.93, 0.86 to 1.01; $p=0.07$). The results of comparisons of different classes of antihypertensive drugs were similar in primary and secondary prevention of stroke.

Beta-blockers and calcium channel antagonists differ in their influence on central BP measured in the aorta. The Conduit Artery Function Evaluation (CAFÉ) substudy of ASCOT BPLA showed greater reduction of central SBP as compared to brachial BP in patients in the amlodipine arm than in subjects on atenolol-based therapy [107]. For a similar effect on brachial BP, amlodipine lowered central SBP by an additional 4.3 mm Hg as compared to atenolol. The influence on central aortic BP might explain the results of the Nordic Diltiazem (NORDIL) trial where, despite lower systolic BP by 3 mm Hg, the number of fatal and nonfatal strokes was significantly higher on beta-blocker than during administration of calcium channel blocker (7.9 vs 6.4 events per 1000 patient-years; $p=0.04$) [108]. Ding et al., performed a meta-analysis including trials that compared beta-blockers with other classes of anti-hypertensive agents in their effect on stroke and central hemodynamics [109]. In nine trials, beta-blockers reduced central aortic pressure (estimated as an Augmentation Index, AI) to less extent than other classes of drugs. The difference in central systolic BP could be largely explained by the heart-rate slowing effect of beta-blockers. In a subsequent meta-regression of these trials , the base-line adjusted change in heart rate by ten beats per minute was associated with a significant increase of AI by 7 %. In outcome trials, odds ratio for stroke was 1.23, which corresponds to the difference in central SBP derived from the above meta-regression analysis.

Calcium channel blockers lower BP acting on resistance arterioles and in a small, but interesting study on stroke outcome, survivors of acute stroke had a lower systemic vascular resistance [110].

Differences between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of stroke were investigated in the meta-analysis including trials in subjects with high cardiovascular risk (ONTARGET), heart failure (ELITE), post-MI (OPTIMAAL, VALIANT) or diabetic nephropathy (DETAIL). Although both groups of drugs reduced BP to the same extent, and there was no difference in the risk of cardiovascular mortality and MI, the risk of stroke was slightly lower with ARBs than ACE inhibitors (odds ratio 0.92; 95 % confidence interval 0.85-0.99; $P=0.037$) [111].

Major clinical trials with different classes of BP lowering drugs in hypertensive populations without previous history of cerebrovascular events (less 5 % of stroke victims at the baseline) are listed in Table 1.

Table 1 Major clinical trials with different classes of BP lowering drugs in hypertensive population without previous history of cerebrovascular events (less 5 % of stroke victims at the baseline)

Trial [ref]	No of participants		Mean age (yrs)	Main drug / comparator	Average reduction in blood pressure (mm Hg)		Number of strokes	
	treatment	control / comparator			systolic	diastolic	treatment	Control/ comparator
ABCD-2[117]	237	243	59	iACE/CcCB	7.4	6.0	4	13
ADVANCE [118]	5569	5571	66	any	5.6	2.2	215	218
Australian TTMH [119]	1721	1706	50	D/plac	-	5.6	13	22
BBB [120]	1063	1063	60	any	8.7	7.1	8	11
CAPPP [121]	5492	5493	52	iACE/plac	-	-	193	149
CONVINCE [81]	8241	8361	66	CaCB/bB+D	0.1	0.7	133	118
DREAM [122]	2623	2646	55	iACE/plac	4.3	2.7	4	8
EWPHE [123]	381	396	72	D/plac	21	8	27	39
FEVER [124]	4841	4870	62	CaCB/plac	4.2	2.1	177	251
HEP [125]	408	459	69	D+bB/plac	11	18	18	38
HDFP [126–128]	5349	5317	51	D/plac	-	5.3	87	142
HOT [129]	12526	6464	62	any	2.8	3.0	200	94
Hunan province [130]	1040	1040	52	CaCB/plac	8.8	5.6	37	79
HYVET pilot [131]	426	426	84	D/plac	22	11	6	18
	431		84	iACE/plac	23	11	12	-
HYVET [48]	1933	1912	84	D/plac	15	6.1	51	69
LIFE [132]	4605	4588	66	ARB/bB	1.1	-0.2	232	309
MRC-1[133]	4297	8654	52	D/plac	13.2	6.1	18	109
	4403		52	bB/plac	9.5	4.9	42	-
MRC-2 [134]	1081	2213	70	D/plac	16.4	7.0	45	134
	1102		70	bB/plac	14.1	7.3	56	-
NORDIL [108]	2786	2805	60	CaCB/D+bB	3.1	0.2	200	236
Oslo [135]	406	379	45	D/plac	16.7	9.8	0	5
PREVENDIT [136]	431	433	51	iACE/plac	3.8	2.9	1	10
SHEP pilot [137]	443	108	72	D/plac	15	4	11	6
SHEP [138]	2306	2331	72	D/plac	13.0	4.3	97	155
STOP [139]	781	780	76	D+bB	8.1	19.5	28	49
STOP - 2 [140]	2213	2196	76	D+bB/CaCB	1	0	86	83
	2213	2205		D+bB/iACE	1	0	86	86
Syst-Eur [141]	2398	2297	70	CaCB/plac	10	4.5	47	77
Syst-China [142]	1253	1141	67	CaCB/plac	8.3	3.1	45	59
TOMHS [143]	668	234	55	any	6.8	3.7	-	-
UKPDS 38 [144, 145]	758	390	56	any	10	4	17	34
UKPDS 39 [145]	400	358	56	iACE/bB	11	6	21	
USPHS [146]	193	196	44	D+Res/plac	9.8	18.0	1	6
VA-1[147]	73	70	51	D+Res+Hdr/plac	27	38	1	3
VA-2 [148]	186	194	51	D+Res+Hdr/plac	18.6	31.3	5	20
VANHLBI [149]	508	504	38	D	-	5.9	0	0

D- thiazide, bB - β blocker, iACE - ACE inhibitor, ARB – angiotensin II receptor antagonist, CaCB - calcium-channel blocker, Res- rauwolfia, Hdr – hydralazine, plac - placebo

Visit-to-visit BP variability is a predictor for future stroke and in the ASCOT BPLA trial this parameter was greater in the atenolol than in the amlodipine group [91]. Webb et al., using data from 389 trials analyzed the effect of different classes of antihypertensive drugs on BPV [92••]. Compared with other drugs, interindividual variation in SBP was reduced

by calcium-channel blockers and non-loop diuretic drugs, and increased by ACE inhibitors, ARBs and beta-blockers. Compared with placebo only, interindividual variation in SBP was reduced the most by calcium-channel blockers. In another study, they analyzed within-individual visit-to-visit variability using data from two trials: ASCOT BPLA comparing atenolol and amlodipine-based regimens and the Medical Research Council (MRC) comparing atenolol-based with diuretic-based BP lowering therapy [112]. In patients during the MRC study, BPV increased on beta-blocker treatment comparing to placebo and diuretic. Subsequent temporal trends in variability in blood pressure during follow up in the atenolol group correlated with trends in stroke risk. In ASCOT BPLA, variability decreased over time in the amlodipine group and increased in the atenolol group. The authors conclude that the opposite effects of calcium-channel blockers and beta-blockers on variability of blood pressure account for the disparity in observed effects on risk of stroke and expected effects based on mean blood pressure. The effects of calcium channel blockers on BPV persisted when they were used in combination with other agents [113].

However, in the above mentioned studies atenolol was given once daily despite its relatively short half-life of 6-7 hours. Limited duration of BP lowering effect of atenolol could cause episodic hypertension and increased BPV. Comparison of different beta-blockers showed that beta1-selective is associated with lower BPV than are the non-selective beta-blockers. Among vasodilating beta-blockers, carvedilol (non-selective) increases BPV, while nebivolol (selective) does not affect BPV [114].

The reduction in BPV was also associated with the frequency of headaches. In a systematic review of randomized trials it was demonstrated that antihypertensive treatment reduced the incidence of headache compared to placebo, but there were significant differences in the magnitude of the effect, independent of reduction in systolic BP [115]. Beta-blockers reduced headache more than other classes and calcium channel blockers did not reduce headache compared to placebo and increased it compared to other drug classes. The mechanism underlying these findings and their clinical significance is unknown.

According to the studies on BPV and stroke prevention, an ideal antihypertensive drug should reduce both mean blood pressure and variability.

Conclusions

Hypertension is the most important modifiable risk factor for stroke and according to the WHO Global Report, 54 % of cerebrovascular incidents are attributable to high BP (SBP>115 mm Hg) with half of them related to sustained hypertension (>140/90 mm Hg). The association between BP and the stroke risk is continuous without any evidence of a threshold down to at least 115/75 mm Hg. Hypertension increases the risk for both ischemic and hemorrhagic stroke, both in subjects without or with the history of coronary heart disease or previous stroke. ABPM is not only a better predictor of stroke risk than office BP, but also can identify disturbances in diurnal variation of BP. Absence of nocturnal drop ("nondipping") or excessive fall of nighttime BP (extreme dippers), early morning acceleration in BP after leaving the bed ("morning surge") are especially associated with cerebrovascular disease. Only ABPM or HBPM can detect two forms of hypertension: - "white coat" and "masked" hypertension – and both carry an increased risk of cardiovascular complications, including stroke.

Increased variability in BP is a risk factor of stroke independent of means BP. In a series of secondary analysis of data from clinical trials, Webb and Rothell reported a significant association between BPV and efficacy of different classes of antihypertensive medications in primary and secondary stroke prevention. However, their data are disputable since they extrapolated data from between patients BP variability, as a measure of within patient BP variability.

It is suggested that lower efficacy of beta-blockers for stroke protection may result from their inferior effect on BPV and central aortic pressure; however, most of the data comes from the studies with atenolol, dosed in a manner not offering a smooth and long lasting lowering of BP. There are many unresolved issues regarding optimal stroke protection. The issue of J-curve and goal BP in primary and secondary prevention is still debated, and data from clinical trials are very limited. However, recent data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) observational study, which included 13,948 patients, generate a hypothesis that for all patients older than 55 years of age, the recommended level of systolic blood pressure should be less than 140 mm Hg, with optimal values possibly between 120 and 139 mm Hg [116]. According to the current state of knowledge, in patients without coronary heart disease, it seems we are justified in loweingr BP even below 130/80 mm Hg, yet this is not recommended in current guidelines. Also, there is no clear indication to guide our treatment based on BP variability or disturbances of diurnal BP rhythm.

Compliance with Ethics Guidelines

Conflict of Interest Zbigniew Gaciong, Maciej Siński, and Jacek Lewandowski declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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