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REVIEW

Blood pressure variability over 24 h: prognostic implications and treatment perspectives. An assessment using the smoothness index with telmisartan–amlodipine monotherapy and combination

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In-office blood pressure (BP) measurements have recognized limitations, including the inability to collect BP information over a long period of time, and during an individual's usual daily activities. Home or ambulatory BP monitoring (ABPM) may therefore be used to complement conventional office measurements, thereby improving prognostic value. Of particular relevance is the ability of 24 h ABPM to quantify the degree of BP variability over 24 h, which has been shown to be a significant and independent risk factor for cardiovascular (CV) morbidity and mortality. Twenty-four hour BP variability is indeed strongly associated with clinical outcomes, and the ability of ABPM to provide a quantification of BP throughout the 24-h period during an individual's normal daily routine is one of the reasons for its high prognostic value. The smoothness index (SI) provides a useful measure of antihypertensive treatment efficacy over the 24 h dosing period, its values being highest with antihypertensive agents that have large and consistent effects across 24 h. Telmisartan and amlodipine are long-acting antihypertensive drugs that, in combination, not only reduce 24 h mean BP more than the respective monotherapies but also provide a significantly greater SI. The provision of homogeneous 24 h BP control has important clinical implications. Maintaining smooth BP over the entire 24 h dosing period may contribute to the improvement of CV outcomes, and reductions in BP variability may decrease end organ damage, and reduce CV risk.
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INTRODUCTION

The importance of effective blood pressure (BP) control to reduce cardiovascular (CV) morbidity and mortality has been strongly reinforced by extensive epidemiologic evidence over the past 30 years. The assessment of a patient's BP may be performed using different methods, including in-office BP (OBP) measurement, home BP monitoring (HBPM) or ambulatory BP monitoring (ABPM) over 24 h. It is now understood that the measurements acquired during office visits do not provide a comprehensive understanding of an individual's BP profile and may be of limited prognostic value,[1] which highlights the need for regular out-of-office BP monitoring in clinical practice, to complement conventional OBP measurements.[2,3]

An important aspect of the information provided by ABPM is the ability to quantify the degree of BP variability over 24 h, which has been shown to be a significant and independent risk factor for CV morbidity and mortality.[4–6] BP variability includes both short-term and circadian components; the latter of which consists of BP reduction during sleep, a feature that may exhibit great inter-individual variability, and an early morning rise that coincides with the peak incidence of CV events.[7]

This review will summarize the latest evidence on ABPM in treated hypertensive patients, including its relationship to clinical outcomes. It will emphasize the value of the smoothness index (SI) as an independent measure of the effects of treatment on 24 h BP profile, with implications for protection against hypertension-related organ damage. The review will conclude by examining the effects of antihypertensive drugs on 24 h BP profile, illustrating these with recent data that demonstrate the effective reduction of BP variability by two long-acting drugs, telmisartan and amlodipine, alone and in combination.

OFFICE *VS.* AMBULATORY BP MEASUREMENTS

Conventionally, BP assessment is based on measurements taken in-office.[3] However, BP is a highly variable physiologic parameter that

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typically fluctuates markedly over 24 h, in both normotensive individuals and in those with treated or untreated hypertension, making isolated office BP readings unable to describe the BP patterns of a given patient accurately.[8] The ability of isolated office readings to reflect patients' prevailing BP levels faithfully is further impaired in subjects with so-called 'white-coat hypertension', also termed 'isolated office hypertension', characterized by an elevation in OBP associated with normal home and/or ambulatory BP values. This phenomenon may be related to an emotional alarm reaction to having readings taken by a doctor or nurse in a clinical setting.[1,9] Similarly, the reverse phenomenon of 'masked hypertension', whereby a patient exhibits a normal clinic BP associated with elevated home or ambulatory BP values, may also result in diagnostic or treatment errors and contribute to elevated CV risk.[3,9,10] Both white-coat and masked hypertension are frequent clinical entities that cannot be identified through office measurements alone and may be responsible for a large number of incorrect diagnoses.[11] White-coat hypertension is present in an estimated 15–20% of patients and masked hypertension has an approximate prevalence of 10–15%.[10,12,13] Therefore, reliance solely on occasional OBP measurements may result in both inaccurate diagnosis and inappropriate treatment decisions in a substantial proportion of patients.

Fluctuations in BP are the product of complex and intricate interactions between behavioral, humoral, central and reflex neural influences.[14–16] Variability in BP is especially marked in patients with a history of previous transient ischemic attack or stroke, making an accurate BP evaluation from single office measurements particularly challenging in these patients.[17] OBP measurements may be susceptible not only to temporal variability of BP within individuals but also to variations in technique (for example, observer bias, digit preference) or non-adherence to recommended BP measuring protocols. Given the dynamic nature of BP and the procedural limitations of in-office readings, a diagnosis of hypertension based exclusively on physician's office readings may thus not always be satisfactory.[18–20]

Technologic developments have enabled more practical measurement outside of the clinician's office. HBPM involves semiautomated measurements that are initiated by the patient, and may be performed daily, over the 7 days preceding any clinic or office visit, typically in the morning and evening,[1,10] thus providing information on average daily life BP levels, on their day-by-day variability as well as on long-term BP control in treated patients. ABPM provides automated BP readings in daily life conditions, making it possible to take numerous oscillometric BP measurements throughout the day, while patients engage in their routine activities, as well as during night-time sleep. Both approaches are strongly supported by current guidelines as they may circumvent some of the limitations of OBP measurements,[1,2,10] particularly in cases of suspected white-coat or masked hypertension. In addition, these methods of BP measurement are not susceptible to observer bias.[2,18,21]

Antihypertensive treatment has differential effects on OBP measurements and 24 h ABPM.[22] Typically, the effect of antihypertensive treatment is greater on OBP measurements than on 24 h average ABP values, and is unevenly distributed between day and night. This suggests that a more systematic adoption of ABPM in clinical trials should be implemented, as ABPM adds valuable information to OBP readings, in particular when assessing the homogeneity of BP reduction in daily life induced by antihypertensive treatment.

PROGNOSTIC VALUE OF 24 h ABPM

There is substantial evidence to indicate that markers of target organ damage linked to hypertension (for example, left ventricular (LV) hypertrophy, LV systolic and diastolic dysfunction, micro-albuminuria, cerebral lacunae at nuclear magnetic resonance imaging, carotid wall thickness and structural alterations of micro-vessels) are more closely and reliably correlated to 24 h average ambulatory BP values than to occasional OBP readings.[23–28] Monitoring BP over 24 h is also a better predictor of clinical outcomes, as shown in the Systolic Hypertension in Europe (Syst-Eur) trial. Although a 10-mm Hg higher conventional systolic BP (SBP) at randomization in Syst-Eur was not associated with a worse prognosis, a 10-mm Hg higher 24 h BP was associated with an increased hazard rate of most CV outcome measures.[18] In the Office *vs.* Ambulatory blood pressure (OvA) study, ABPM provided additional predictive information in relation to CV outcomes in treated hypertensive patients, after adjustment for OBP values.[26] A large prospective study of 5292 untreated hypertensive patients referred to a single BP clinic further verified the superiority of ABPM over OBP values in predicting CV mortality.[27]

Although 24 h ABPM is evidently a useful marker in a clinical trial setting, there is as yet only limited application of this technique in clinical practice. The international Ambulatory blood pressure Registry: TEleMonitoring of hypertension and cardiovascular rISk project (ARTEMIS) is the first international ABPM registry,[29] which aims to provide information on the real level of out-of-office BP control and CV risk reduction for hypertensive patients worldwide. The ARTEMIS database presently includes more than 15 000 hypertensive patients from 41 different countries over five continents. Through a series of research studies focusing on ABPM, ARTEMIS aims to promote the correct use and interpretation of out-of-office BP monitoring techniques in clinical practice, with an ultimate aim of improving both BP control in daily life and disease management in hypertension.

BP VARIABILITY OVER 24 h AND RELATIONSHIP TO CLINICAL OUTCOMES

BP variability is linked to elevated mean BP levels—an increase in the latter typically being accompanied by an increase in the former. Nevertheless, BP variability does appear to contribute independently to CV risk, over and beyond the effect of elevated mean BP levels.[4,19,30,31] For example, patients with greater than 15-mm Hg s.d. of daytime SBP are at a significantly increased relative risk of the development of early atherosclerosis and CV events, independent of their absolute BP levels.[32] Some specific features of the 24 h BP variability are of interest, not only because they cannot be detected by office BP measurements but also because they are associated with target organ damage and the risk of cardiac and cerebrovascular events. The early morning BP 'surge' (EMBPS), a transient increase in both SBP and diastolic BP (DBP) during the morning hours around the time of rising,[8] is one pattern of variability linked to poor prognosis.[33] For example, a cross-sectional study in 743 patients found a strong correlation between target organ damage and the EMBPS at the time of rising.[34,35] A 10-mm Hg increase in the EMBPS has been shown to increase stroke risk by 22%, independent of age and average 24 h BP.[36] This phenomenon is of clinical significance as poor control during the early morning hours is very common, even in patients who have apparently controlled in-clinic BP.[37–39] Antihypertensive treatment that is able to achieve sustained BP control might blunt the EMBPS and help to reduce the incidence of these events.[40]

As well as early morning fluctuations, BP patterns during the night-time are also important and may even be of greater prognostic significance. Night-time BP patterns vary greatly from one patient to another. A number of clinical trials have demonstrated that a higher

nocturnal BP and an increased night-to-day SBP ratio are both independent predictors of CV events, suggesting that night-time BP is an important and independent contributor to the overall BP load on the CV system.[18,32,41–43] In the general population, BP falls by ~10–20% of daytime values during sleep, a phenomenon known as 'dipping'. In some hypertensive subgroups, this nocturnal drop may be drastically reduced or even abolished, leading to a so called 'non-dipping' phenomenon, which has been associated with a greater prevalence of subclinical organ damage, increased CV risk and stroke.[42] The causes of nocturnal non-dipping are not clear, although obstructive sleep apnea may be responsible in some patients, and non-dipping is more common in patients with diabetes mellitus.[44–46] Damage to autonomic CV regulation in diabetes mellitus or the presence of organ damage may impair the ability of vessels to dilate and this may affect circadian BP fluctuations.[47,48] It is believed that non-dipping is also associated with more rapid decline in renal function in diabetic nephropathy.[49]

A further subgroup of patients may exhibit inverse dipping, also termed nocturnal BP rising, with a nocturnal BP increase compared with daytime BP. This phenomenon is associated with a poor prognosis for stroke and CV events.[50]

In other hypertensive patients, termed 'extreme dippers', the night-time BP reduction may be highly pronounced, with BP falling more than 20% lower than the daytime BP.[51] Extreme dippers tend to have greater variability of BP than dippers and are at risk for non-fatal ischemic stroke and silent myocardial ischemia,[47,50] although this finding has not been confirmed in all studies and it is not clear whether this increased risk is related to the excessive night-time drop in BP or to the related large EMBPS that occurs upon rising.

On the basis of the evidence gathered over the past decade regarding these features of BP, it has been suggested that drugs capable of providing smooth 24 h BP control, or of reducing BP variability, may protect against target organ damage.[4,19,52] In non-dipper or reverse dipper patients, improving the nocturnal BP decline through proper titration and scheduling of antihypertensive treatment might improve prognosis by specifically reducing the risk of CV events and stroke.[42] Homogeneous BP control has been directly correlated with treatment-induced regression of LV hypertrophy as well as to a slower progression of carotid atherosclerosis, further demonstrating the clinical importance and relevance of smooth 24-h BP control.[53–55]

ASSESSMENT OF TREATMENT EFFICACY IN REDUCING BP VARIABILITY OVER 24 h

Two different approaches have been used to assess the ability of a given treatment to induce a smooth reduction of BP over 24 h, leading to a reduction in 24 h BP variability: the assessment of trough:peak (T:P) ratio and the estimate of the smoothness index (SI).

The T:P ratio during 24 h is an index of the distribution of BP reduction offered by a particular drug over 24 h and indicates the duration of the antihypertensive effect of drug treatment.[56,57] The trough value used is the mean change in SBP and DBP during the final hours of the 24 h dosing period (for example, in the 2 h before next dosing) and the peak value is defined as the mean change in SBP and DBP during the period when the BP change is maximal (for example, 2–8 h post dosing).[56,58] In a study, the overall group T:P ratio may be obtained by either dividing the mean change in trough BP by the mean change in peak BP or by calculating the median (plus the upper and lower quartile and the extreme values of the distribution) of the individual T:P ratios. The latter approach may be used because the individual T:P ratios do not show a normal distribution. An illustrative selection of T:P ratios for some antihypertensive agents is depicted in Table 1. A high T:P ratio with a value close to 1 is an indication of a long duration of action and optimal therapeutic coverage for 24 h or even longer. However, although the T:P ratio has some utility in comparing average 24 h efficacy of drugs or combinations in groups of patients, it is a fairly crude measure of BP variability in treated patients and cannot be used individually given its limited reproducibility and its susceptibility to behavioral influences over the narrow time intervals where it is computed. Because of this limitation, it may lead to extreme values in both directions when calculated for an individual patient, when the peak or the trough effect is close to zero, for example.

Table 1 SBP trough-to-peak ratios for antihypertensive monotherapies

Drug class	*Monotherapy*	*SBP T:P ratio or range thereof*	*$t_{1/2}$, or range thereof (h)*	*Source*
ARB	Azilsartan	0.95[a]	11	58, 81
	Telmisartan	0.92[b]	Up to 24	62, 82
	Candesartan	0.82[a]	9	58, 83
	Olmesartan	0.60–0.80[c]	13	65, 65
	Valsartan	0.65[a]	6	66, 84
	Losartan	0.62[a]	2 (6–9 for metabolite)	62, 85
	Irbesartan	0.57[a]	11–15	62, 84
CCB	Amlodipine	0.85[a]	35–50	70, 86
	Diltiazem SR	0.20–0.80[a]	6–8	87, 88
	Nitrendipine	0.10–0.80[a]	12–14	87, 89
ACE inhibitor	Lisinopril	0.63[d]	12.6	90, 91
	Ramipril	0.50–0.63[a]	13–17	87, 92
	Captopril	0.25[a]	2	87, 93

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; SBP, systolic blood pressure; SR, sustained release; $t_{1/2}$, plasma elimination half-life; T:P, trough:peak ratio.
[a]Mean values.
[b]Ratio of reduction in trough BP to reduction in maximal diurnally-adjusted BP.
[c]Not mentioned.
[d]Median value.

The SI provides a measure of the consistency and magnitude of BP reduction by a given treatment throughout 24 h. To calculate the SI, the mean of the 24 hourly changes in BP from baseline (ΔH_{0-24}) is divided by its own s.d., that is, $\Delta H_{0-24}/s.d._{\Delta H}$, (Figure 1).[53] A high SI with a value greater than 1 is most desirable, indicating a large but also consistent BP reduction. The SI has been shown to be significantly affected by ethnicity, sex, smoking status, age and baseline 24 h mean BP.[59] The SI for systolic and diastolic ABP was lower in men, black patients, smokers and those who were older or had lower baseline BP. For both mono and combination therapy, SI was higher with increased baseline 24 h mean BP (both $P<0.0001$), and lower with higher baseline 24 h ABP variability (both $P<0.0001$).[59] The SI is also an indirect index of the occurrence of a reduction in BP variability during treatment, its values being inversely related to BP variability under treatment, with the latter being assessed by the s.d. of 24 h average BP.[53]

The SI has also been shown to be an independent predictor of treatment-induced reductions in target-organ damage. The SI may indeed have a higher predictive value than other BP-derived parameters. For instance, two studies have found a correlation between treatment-induced reductions in LV mass index and SI, but not with changes in office BP, with mean 24 h ABPM values, or with the T:P ratio.[53,60] Likewise, correlation has been identified between changes in

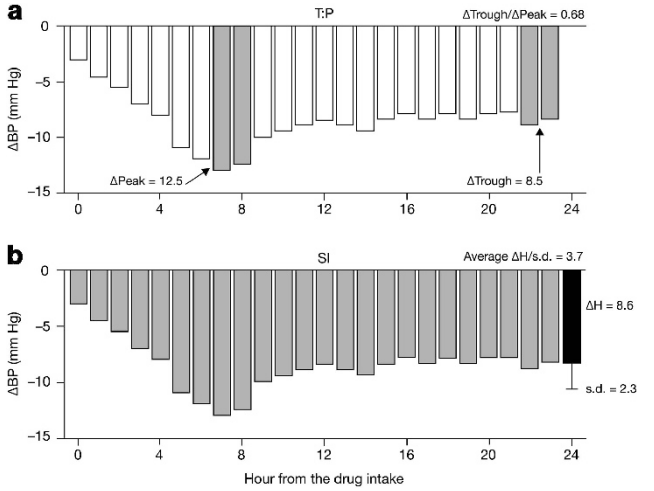

Figure 1 Examples to illustrate calculation of the (**a**) trough-to-peak ratio and (**b**) SI from hourly BP values obtained before and during treatment (using ABPM). BP, blood pressure; ΔH, average of treatment-induced BP reductions from baseline for each hour; s.d., standard deviation of the average hourly blood pressure reductions; SI, smoothness index; T:P, trough:peak ratio.

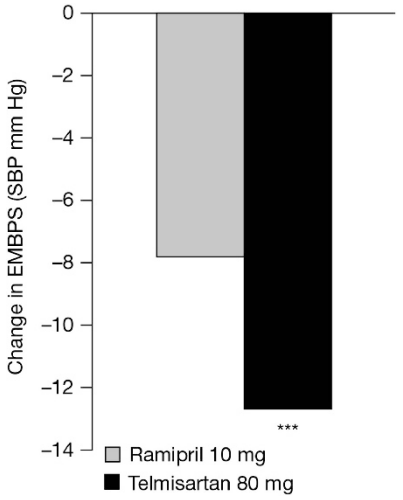

Figure 2 Reduction of the EMBPS with telmisartan 80 mg or ramipril 10 mg. EMBPS, early morning blood pressure surge; SBP, systolic blood pressure. ***$P=0.0001$ *vs.* ramipril.

carotid artery wall thickness during therapy and the treatment effect on SI, but not with changes in T:P ratio, or absolute 24-h BP reductions.[55]

EFFECTS OF ANTIHYPERTENSIVE TREATMENT ON SI

Available antihypertensives vary widely in their duration of action, as a consequence of pharmacodynamic and pharmacokinetic differences.[61] To illustrate how drugs with a long duration of action can affect measures of 24 h variability, we have examined 24 h ambulatory BP data from clinical trials of the angiotensin II receptor blocker, telmisartan and the calcium channel blocker (CCB), amlodipine. Both of these drugs have specific pharmacologic and pharmacokinetic characteristics that make them suitable for providing consistent BP reductions throughout the 24 h dosing period. Telmisartan has a longer plasma half-life and receptor dissociation half-life than other angiotensin II receptor blockers currently available.[62–64] The elimination half-life of telmisartan is ~24 h,[62] compared with 13 h for olmesartan,[65] 11–15 h for irbesartan[62] and 6 h for valsartan.[66] On the basis of these characteristic features, it is therefore not surprising that telmisartan has been shown to provide sustained 24 h BP reduction. Telmisartan 80 mg provided significantly greater BP reductions compared with valsartan 160 mg, particularly during the last 6 h of the 24 h dosing interval when incidences of BP-related complications are at their highest.[7,67] A large practice-based study in more than 25 000 hypertensive patients showed that telmisartan either alone or in combination with a thiazide diuretic reduced the EMBPS and reduced home BP variability throughout the day.[68] Telmisartan reduces the EMBPS to a greater extent than the angiotensin-converting enzyme inhibitor, ramipril (Figure 2).[69]

Of the CCBs currently available, amlodipine has the longest elimination half-life, of 35–50 h,[70] compared with 19 h for lacidipine,15–20 h for felodipine and 2–7 h for verapamil, diltiazem and nifedipine.[71,72] Amlodipine, like telmisartan, also has slow receptor dissociation kinetics.[73] Amlodipine through gradual and prolonged reduction in BP due to long-lasting vasodilation may be associated with less reflex tachycardia and reduced likelihood of

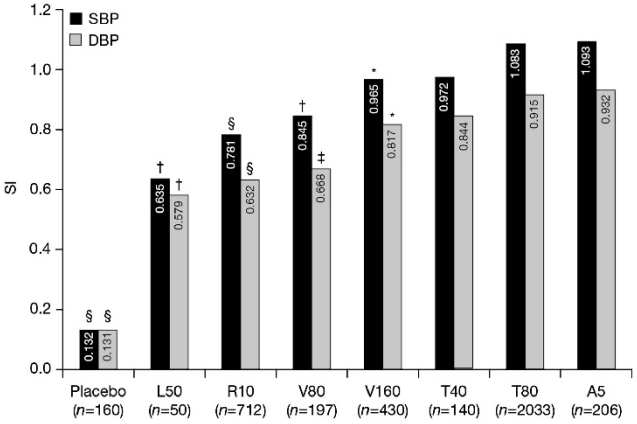

Figure 3 Comparison of the 24 h SBP/DBP SIs for seven antihypertensive monotherapies. A5, amlodipine 5 mg; DBP, diastolic blood pressure; L50, losartan 50 mg; R10, ramipril 10 mg; SBP, systolic blood pressure; T40, telmisartan 40 mg; T80, telmisartan 80 mg; V80, valsartan 80 mg; V160, valsartan 160 mg. *$P<0.05$; †$P<0.01$; ‡$P<0.001$; §$P<0.0001$ *P*-values indicate lower SI *vs.* telmisartan 80 mg. Data are based on nine trials involving 3928 monotherapy-treated patients.

negative inotropic effects.[72] Both telmisartan and amlodipine are effective in improving the SI in monotherapy. A meta-analysis of 5188 patients in 11 randomized, controlled studies used the SI to evaluate and compare the 24 h antihypertensive efficacy of telmisartan, losartan, valsartan, ramipril, amlodipine or a combination of angiotensin II receptor blocker plus hydrochlorothiazide. This analysis showed that telmisartan 80 mg and amlodipine 5 mg have a similar SI, which was higher than that of other angiotensin II receptor blockers and of ramipril (Figure 3).[59] Across the CCBs, the 24 h SI value for amlodipine 5 mg in the meta-analysis[59] was higher than those of manidipine and lercanidipine in patients with mild-to-moderate hypertension,[74] nifedipine gastrointestinal therapeutic system (GITS) in patients with essential hypertension,[75] felodipine in elderly patients[76] and was lower than that of diltiazem 180 mg in patients with essential hypertension.[77]

A *post hoc* analysis of two large randomized trials, the Anglo Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) and the Medical Research Council, found that both short- and long-term between-visit BP variability was lower in hypertensive patients treated with amlodipine compared with atenolol.[52] A lower risk of stroke and coronary events was observed in patients treated with amlodipine, and the low BP variability seen with amlodipine treatment may at least in part explain the reduced risk of stroke in this group.

It is now widely accepted that, in order to achieve effective and sustained control of BP, many hypertensive patients will need combination therapy using antihypertensive agents of different classes, preferably with complementary mechanisms of action.[2,3] Combinations of renin–angiotensin system inhibitors with CCBs are commonly used in clinical practice because their complementary modes of action provide good BP lowering and a lower incidence of peripheral edema than CCB monotherapy.[78]

In combination, telmisartan and amlodipine give increased BP reductions when assessed by both in-office measurements and by 24 h ABPM.[78] In a randomized, controlled, 4×4 factorial design study, 1461 patients received telmisartan (20, 40 or 80 mg) in combination with amlodipine (2.5, 5 or 10 mg).[78,79] In a recent *post hoc* analysis of this study, SIs were calculated for the 440 patients receiving clinical doses of these agents (amlodipine 5 or 10 mg, telmisartan 40 or 80 mg). The patients in this analysis were mostly <65 years old (86.6%; mean age 53 years) and their 24 h mean ambulatory BP at baseline was 143.1/87.4 mm Hg. This analysis demonstrated for the first time the dose-dependency of the SI and the magnitude of the effect that can be expected from treatment with a combination of two long-acting agents (Figure 4).[80] Improvements of the SI were significantly greater with all combinations (except the lowest dose T40/A5) than with either monotherapy, and the SI achieved with the highest-dose combination (telmisartan 80 mg/amlodipine 10 mg) was around twice the SI achieved with amlodipine monotherapy. This is in line with the effects observed in this study on 24 h average ambulatory BP values (mean SBP/DBP reductions from baseline in 24 h ABPM for telmisartan 80 mg/amlodipine 10 mg were –22.4/–14.6 mm Hg, compared with –11.9/–6.9 mm Hg for amlodipine 10 mg and –11.0/–6.9 mm Hg for telmisartan 80 mg monotherapies ($P<0.0001$ for each comparison)).

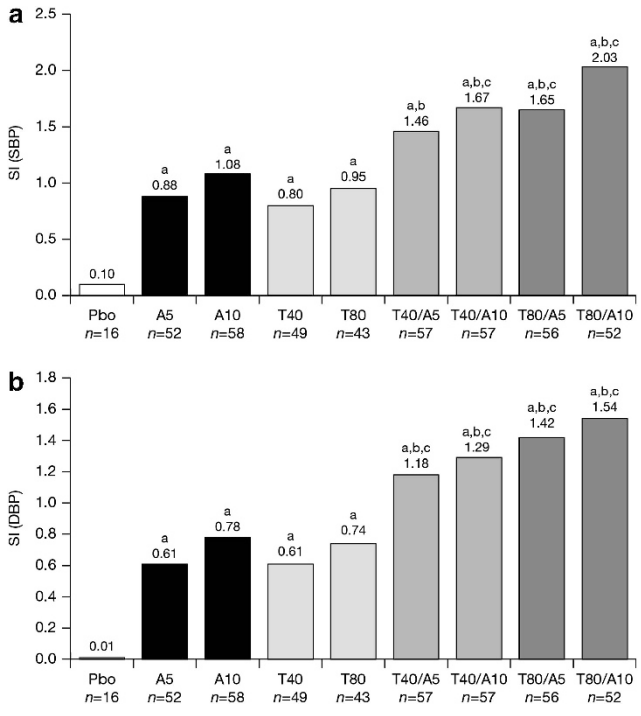

Figure 4 Summary of 24-h SBP (**a**)/DBP (**b**) SIs, using telmisartan and amlodipine either as monotherapy or in combination. A5, amlodipine 5 mg; A10, amlodipine 10 mg; DBP, diastolic blood pressure; SBP, systolic blood pressure; T40, telmisartan 40 mg; T80, telmisartan 80 mg. [a]Significant *vs.* placebo; [b]Significant *vs.* corresponding monotherapies; [c]Significant *vs.* all monotherapies.

CONCLUSIONS

Both the magnitude of BP reductions and the control of BP variability may be important in the prevention of CV and cerebrovascular events. ABPM provides an opportunity to obtain measurements of BP throughout the 24 h period during an individual's normal daily routine, and its use is therefore recommended in many patients (94) to complement conventional OBP measurements.

The SI is a useful measure that integrates the assessment of mean BP reductions with the assessment of the degree of concomitant reduction in BP variability, offering a comprehensive evaluation of treatment effects on BP throughout a 24 h period, with antihypertensive agents characterized by large and consistent effects across 24 h having the highest SI values.

The SI can be used to compare the 24 h BP-lowering profiles of different drugs and drug combinations. The combination of telmisartan and amlodipine, which have pharmacokinetic characteristics that make them suitable for providing consistent BP reductions throughout the 24 h dosing period, has been shown not only to reduce 24 h mean BP more than the respective monotherapies but also to yield SI values significantly greater compared with the SIs observed with either monotherapy. These findings support guideline recommendations for the use of combination therapy for most patients whose BP is above goal, and further suggest that such a combination should employ long-acting agents when possible, as these help to maintain a homogeneous and smooth 24 h BP profile. The provision of homogeneous 24 h BP control has important clinical implications. Maintaining smooth BP over the entire 24 h dosing period may contribute to the improvement of CV outcomes, and reductions in BP variability may decrease end organ damage and reduce CV risk.

The use of ABPM and HBPM are already strongly supported by clinical hypertension guidelines.[94] HBPM is easier to use, which helps physicians and patients maintain better control, track treatment also over a long-term follow-up and reduce clinic visits, but HBPM does not have the ability to track nighttime BP, which is an independent predictor of CV risk. Although the use of ABPM has increased over the years, there remains a need for more information and guidance on 24 h ambulatory BP techniques in clinical practice. The ARTEMIS project will help to promote best practice in ABPM in order to improve disease management and CV risk reduction.

CONFLICT OF INTEREST

Dr Parati declares no conflict of interest in relation to this paper. In particular, none of the following situations occurred over the last year: received 1 000 000 yen or more for employment, supervising or advisory position; given stock or stock options worth 5% or more of the total share or generating profit of 1 000 000 yen or more; received patent royalties or licensing fees of 1 000 000 yen or more; received honoraria of 1 000 000 yen or more for lectures, article contributions or such activities to support promotional activities; received

research funding of 2 000 000 yen or more; outside research activities, given travels, gifts or any other benefit worth 50 000 yen or more. Dr Schumacher is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

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