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Stabilizing blood pressure variability: a new therapeutic target in hypertension

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Blood pressure variability (BPV), recognized for many years as being a risk for cardiovascular outcome, has recently become a focus of attention because of a number of studies showing that increased variability predicts cardiovascular outcome, especially stroke, and that different drug classes may affect variability, either beneficially, by reducing it, or detrimentally, by increasing it. The recent literature emphasizes the importance of reducing mean blood pressure levels, as is recommended in all the guidelines; however, physicians are now obliged to consider drugs, such as calcium channel blockers, that have been shown to reduce BPV. Prescribing drugs, such as the older β -blockers, which increase BPV, should be carefully considered in the context of the overall cardiovascular status of the patient. The recent introduction of flexipills containing combinations of drugs, such as amlodipine/perindopril, that reduce both mean blood pressure levels and BPV provides the practicing physician with the option of achieving two desirable targets of treatment. The measurement of short-term BPV can be readily achieved with ambulatory blood pressure measurement, whereas the measurement of long-term visit-to-visit variability is not so easily achieved in routine practice.

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In a recent review on blood pressure variability (BPV), Peter Rothwell argues that the management of hypertension has been clouded by the fact that physicians and scientists have been distracted from consideration of variability by giving obsessional attention to mean blood pressure (BP).¹ The hypertension guidelines, which insist on reduction of BP per se and remove BP variability from consideration, may have done science a disservice by obscuring the influence of BPV on cardiovascular outcome. Indeed, though a reduction in BP makes a very valuable contribution to outcome, it does not always account fully for the benefit of therapeutic intervention, which also might be due, in part, to a reduction in BPV.^{1,2} This review will examine the role of BPV, especially for the potential it offers as a new target for treatment.

Blood pressure variability

In discussing BPV, it is important to recognize two forms of variability—short-term BPV, which is the variability of BP over minutes or hours, such as is seen on 24-hour ambulatory blood pressure measurement (ABPM), and long-term BPV, such as is seen with repeated recordings over weeks or months, and which is often called visit-to-visit BPV.

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◆ Short-term BPV

The prognostic significance of short-term BPV as a predictor of poor cardiovascular outcome has been documented for many years in different cohorts of initially untreated or treated hypertensive subjects,³⁻⁹ and in general populations.^{10,11} If standard deviations are used as a measure of BPV, these are usually around 10-15 mm Hg for the daytime and 5-10 mm Hg for the nighttime periods.¹ Studies of the prognostic value of ABPM have been limited by tending to consider only the mean values of BP, or the day-night differences in BP.¹ The results of these studies have often been conflicting, because of the variety of ways in which BPV is expressed, eg, standard deviation or coefficient of variation; the period selected for the assessment of BPV, eg, day, night, or 24-hour periods; and the blood pressure selected, eg, systolic blood pressure (SBP) or diastolic blood pressure (DBP).¹²

As far back as 1987, Parati's group demonstrated that higher diurnal BPV measured by ABPM over 24 hours was associated with an increased risk of left ventricular hypertrophy.^{13,14} His group has continued to highlight the importance of BPV as a prognostic marker.¹⁵ It has been known for many years that the manifestations of BPV seen during the day and night windows of a 24-hour period, such as nocturnal dipping and the morning surge, are independently related to organ damage and the risk of cardiovascular events.^{16,17} However, in a large population cohort (8938 subjects), though short-term reading-to-reading BPV with ABPM was an independent risk factor, the level of the 24-hour ABPM was the primary BP-related risk factor to be addressed in clinical practice.¹⁸

◆ Long-term BPV

Data from Framingham showing that cardiovascular events did not appear to be related to BPV drew attention away from variability as a risk over the longer term.¹⁹ However, several randomized controlled trials have shown a strong association of longer-term BPV in systolic BP recorded over several visits with stroke and coronary heart disease risk.²⁰⁻²⁵

Rothwell and his colleagues have recently shown that SBP variation over time and from one visit to the next may be associated with a poor cardiovascular prognosis.^{1,26-29} Higher

visit-to-visit variability in SBP was also associated with stroke and coronary events in treated hypertensive patients enrolled in ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm).²⁷ BPV between visits and maximum BP reached in 4 cohorts of patients with previous transient ischemic attacks were strong predictors for subsequent stroke.²⁷ In treated hypertensive patients in ASCOT-BPLA, SBP variation between visits was also a strong predictor of stroke and coronary events, independent of mean clinic BP or APBM. Variation of ABPM was a weaker predictor overall, but this was related to visit-to-visit variability. Patients with well controlled BP, but high residual variability in SBP had a five times higher risk of stroke than did those with low residual SBP variability in ASCOT-BPLA.²⁷

The evidence supporting the influence of BPV on prognosis does not question the importance of lowering BP, as is recommended in all the guidelines, but rather draws attention to BPV as an additional target, which if modified by treatment might confer a benefit above that of reducing BP alone.

The prognostic importance of visit-to-visit BPV has recently received further support from a population-based study in US adults in whom higher visit-to-visit variability in SBP was associated with increased mortality risk over a 14-year follow-up. There was no such association with visit-to-visit variability in DBP.³⁰ This study has some additional strengths, as observed by Mancia.³¹ Firstly, the data analyzed were obtained in a general population distinct from the Rothwell cohorts, which came from clinical trial recruits. Secondly, the study analysis showed that factors, such as female sex, a history of myocardial infarction, diabetes, and several measures of organ damage (albuminuria, estimated glomerular filtration rate, and pulse pressure) also influenced visit-to-visit BPV. Of particular interest, the relationship of visit-to-visit BPV with all-cause mortality was also present in subjects with normal BP, suggesting that visit-to-visit BPV may be a prognostic marker even before BP becomes elevated.³¹

Pathogenic mechanisms of BPV

The main consequence of BPV seems to be its effect on the brain, which is very susceptible to fluctuations in BP. Instability of BP is associated with brain atrophy, subcortical lesions, and cognitive impairment.³² Several hypotheses have been proposed for mechanisms underlying higher levels of visit-to-visit variability in BP.³³⁻³⁵ One of the major factors facilitating BPV may be arterial stiffness.³⁶ Pulse pressure and older age, which are both directly associated with arterial stiffness, have been shown to be independently associated with higher visit-to-visit variability in SBP.^{37,38} The association of arterial stiffness with BPV is further strengthened by the strong association of the ambulatory arterial stiffness index (AASI) with stroke.³⁹ The AASI, which is a measure of the dynamic relation between DBP and SBP throughout the entire day, has been shown to predict cardiovascular mortality in a large co-

SELECTED ABBREVIATIONS AND ACRONYMS

AASI	ambulatory arterial stiffness index
ABPM	ambulatory blood pressure measurement
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm
BP	blood pressure
BPV	blood pressure variability
NHANES	National Health And Nutrition Examination Survey
UK-TIA	United Kingdom Transient Ischemic Attack (trial)

hort of hypertensive individuals. Furthermore, compared with pulse pressure, the AASI is a stronger predictor of fatal stroke in patients with ambulatory normotension than in patients with hypertension. This important association is similar to the finding of a study in which visit-to-visit BPV predicted all-cause mortality in subjects in whom BP was normal,³⁰ suggesting that visit-to-visit BPV may be a prognostic marker even before BP becomes elevated. The importance of these remarkable associations is twofold: first, both BPV and the AASI may predict outcome in patients even before BP becomes elevated, thereby providing a means of identifying patients at risk before they develop hypertension, and second, it is possible that the AASI, which is a measure of short-term BPV obtainable for a single ABPM, might be of equal prognostic importance to visit-to-visit BPV, which is only obtainable from repeated BP measurements.

Other mechanisms that might be accountable for increased BPV include baroreflex regulation of BP,⁴⁰ inflammation,⁴¹ and heart rate variability.⁴² Whereas one study has shown that, in addition to BPV, heart rate variability may also have prognostic significance,⁴² other evidence indicates that decreased (not increased) heart rate variability is associated with an increased risk of mortality, suggesting that heart rate variability does not influence the relationship between BPV and mortality.⁴³

How can BPV be measured?

◆ *Measuring short-term BPV*

ABPM provides numerous values, beyond the arithmetic mean of the measurements, that are not utilized in clinical practice.⁴⁴ The reduction in ABPM variability in ASCOT-BPLA almost mirrors visit-to-visit variability, which suggests that it may be possible, by concentrating on the many measures of variability already available within a single ABPM, to identify an index of ABPM BPV that would be equivalent to visit-to-visit BPV. Measures derived from the linear relationship between systolic and diastolic pressures are believed to be associated with mechanical properties of the arteries, especially with stiffening of the arteries with aging.

As has already been mentioned, the AASI provides a readily accessible measurement of both BPV and arterial stiffness.³⁹ The AASI and its related slope have been shown to predict outcome^{39,45} and target organ damage.^{39,46-48} However, the value of the AASI as a measure of arterial stiffness has been questioned,^{49,50} because of its strong dependence on age, sex, pulse pressure, and nocturnal BP decline.^{50,51} Perhaps more attention should be focused on the prognostic power of the AASI as a measure of BPV rather than on the mechanistic explanation for this association. Various modifications of the AASI have been proposed without much overall advantage over the original index, which is not to say that the incorporation of different mathematical models of the ABPM-derived index will not yield a more robust index.^{52,53}

The appropriateness of standard deviation as an index of BPV has been questioned,^{54,55} because it only reflects the dispersion of values around the mean and does not account for the order in which BP measurements are obtained. An alternative index, named average real variability, which is based on the total variability concept of real analysis in mathematics, and which is sensitive to the individual BP measurement order, has been proposed.^{54,55} This index of daytime SBP has been shown to be an independent predictor of cardiovascular events in hypertensive patients, whereas a high standard deviation is not.⁵⁵

◆ *Measuring long-term BPV*

It is important to note that regardless of how BP is measured, whatever the associations attributed to long-term BPV, they apply only to systolic BP.¹ No association has been shown between visit-to-visit BPV in DBP and all-cause mortality.^{26,3} For example, in the Honolulu Heart Program, variance of DBP across 4 visits was not associated with subsequent coronary heart disease incidence.^{25,26} In addition, in the UK-TIA (United Kingdom Transient Ischemic Attack) study, the visit-to-visit variability in DBP was not associated with stroke, and an association was present only in the highest deciles in ASCOT-BPLA.²⁶

Evidence suggests that visit-to-visit BPV is reproducible and not a random phenomenon. The UK-TIA study and the European Carotid Surgery Trial have shown that reproducibility of visit-to-visit BPV is good.³³ In these studies, BPV was based on a single measurement at each visit; having multiple measurements at each visit results in a higher degree of reproducibility in the level of visit-to-visit BPV.³⁰ However, the confounding effects of BP-measuring techniques and of BP-lowering treatment call for caution in the interpretation of results. For example, in the NHANES (National Health And Nutrition Examination Survey) study, the first set of BP measurements were obtained during an in-home examination, whereas the latter two sets of measurements were obtained during a medical evaluation conducted in a mobile examination center. Furthermore, whereas the in-home BP measurements were obtained by a research assistant, the clinic BP measurements were obtained by a physician.³⁰

In ASCOT-BPLA, BPV in mean daytime SBP on repeated ABPM correlated with visit-to-visit variability in clinic SBP, indicating a contribution from fluctuations in underlying blood pressure. Both within-visit variability in sitting SBP and daytime variability in SBP on ABPM were lower in the amlodipine/perindopril group than in the atenolol/thiazide group, but the latter was a weaker predictor of vascular events than was visit-to-visit variability²⁶ and accounted less well for the reduced event rate in the amlodipine/perindopril group (*Figure 1, page 28*).²⁹ This suggests that the larger variations in BP that are seen from visit to visit better reflect the factor or factors that are causally related to the risk of vascular events. Yet another

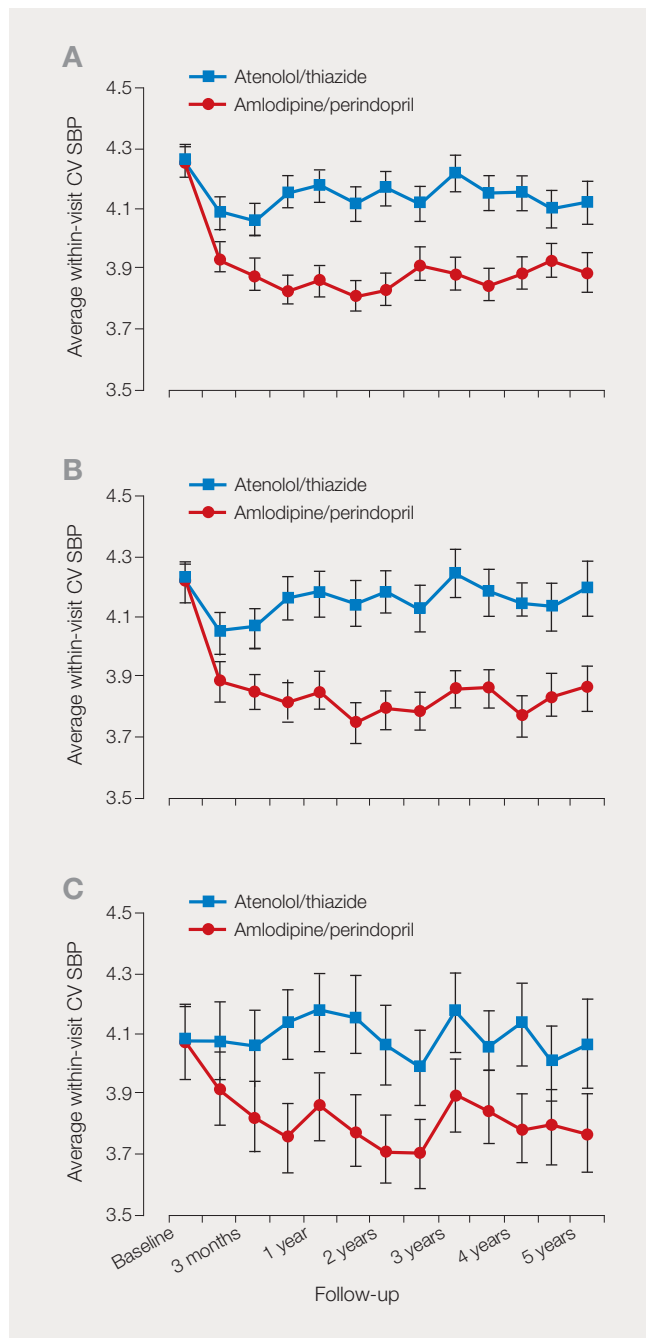


Figure 1. Within-visit variability of systolic blood pressure in ASCOT.

A, All patients. **B,** Patients on treatment. **C,** Patients not on antihypertensive drugs at baseline. Bars are 95% CI.

Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm; CI, confidence interval; CV, coefficient of variation (within-visit variability); SBP, systolic blood pressure.

Modified from reference 29: Rothwell et al. *Lancet Neurol.* 2010;9:469-480. Copyright © 2010, Elsevier.

dictive of stroke than was mean SBP in ASCOT-BPLA and in the UK-TIA trial. Furthermore, the atenolol/thiazide combination was associated with lower minimum daytime SBP and DBP, possibly due to a higher frequency of postural falls, which in the case of DBP might reduce coronary perfusion.²⁹ BPV on ABPM was a weaker predictor of vascular events than was visit-to-visit BPV, and it accounted less well for the reduced event rate in the amlodipine/perindopril group than in the atenolol/thiazide group, suggesting that average variability from minute to minute (best exemplified as average successive variability on ABPM) does not capture elements of variability that are associated with risk of stroke.²⁶ However, this index is as yet untested in standardized conditions and its application and the conclusions inferred must be seen as conceptual rather than proven.

◆ **How can BPV be treated?**

It is clear from a review of the literature that increased BPV, both short-term and long-term, presents a threat for the development of stroke and other cardiovascular events. Hypertension is the most prevalent treatable risk factor for stroke.⁵⁶ The current practice of reducing BP levels to normal throughout the day and nighttime periods is not in dispute. However, control of hypertension continues to be inadequate despite the excellent array of effective, well-tolerated medications.⁵⁷ Recent data from the US indicates that approximately 28% of Americans with hypertension are unaware of their hypertension, 39% are not receiving therapy, and 65% do not have their BP controlled to levels below 140/90 mm Hg (Figure 2).⁵⁷

In Europe, the situation is even worse, where despite knowing for at least two decades the importance of BP control in preventing stroke and having more than enough drugs available to effectively treat hypertension, the “rule of halves” is operative in most European countries^{58,59}: only half the people in society with hypertension are aware that their BP is elevated; of those identified as having high BP, only half are on BP-lowering drugs; and of those receiving treatment, only half are well controlled. To which might be added, if BP control was achieved in those with undiagnosed hypertension or inadequately treated hypertension, the occurrence of stroke could be halved. In the three EUROASPIRE (EUROPEAN Action on Secondary and Primary prevention through Intervention to Reduce Events) studies conducted over a decade in specialized centers in Europe, there was no improvement in BP control despite large increases in prescriptions for all classes of antihypertensive drugs, ie, antihypertensive medication is

er index, the average successive variability index, based on the average absolute difference between successive values, did not predict stroke, and accounted less well for the clinical benefit observed in the amlodipine/perindopril group versus the atenolol/thiazide group than did the standard deviation or coefficient of variation of SBP. It has been suggested that this index measures short-term changes between consecutive BP readings, whereas standard deviation or coefficient of variation, which are influenced by changes over hours and which give more weight to extreme values, are more sensitive to instability in BP related to specific stressors, because maximum SBP in visit-to-visit or ABPM BPV was more pre-

being prescribed, but not being prescribed in sufficient dosage or combination therapy to achieve BP control.⁶⁰ These statistics indicate the need to intensify measures to control BP.

Now, we must focus not only on controlling BP, but also BPV. Whereas randomized controlled trials have shown that lowering BP is effective in the prevention of stroke, recent meta-analyses have suggested that there are important drug-class effects, with calcium channel blockers reducing stroke risk to a greater extent, and β -blockers to a lesser extent, than expected by their observed effects on BP. Thus, it is possible that the differences between drug classes in their effects on stroke risk are caused by effects on some other parameter of blood pressure, such as BPV.^{29,61} Compared with other drug classes, calcium channel blockers and non-loop diuretic drugs have been shown to better reduce interindividual variation in SBP.²⁸ Atenolol/thiazide-based treatment and amlodipine/perindopril-based treatment had opposite effects on within-individual BPV, for within-visit, visit-to-visit, and ABPM, independent of their effects on BP. Moreover, the reduced event rates in the amlodipine/perindopril group in ASCOT-BPLA, which could not be fully accounted for by changes in BP or in other risk factors, can be explained by the beneficial lowering of systolic BPV.²⁸

Stabilization of BPV is a potentially important target for drug development and combination therapy, and new drugs or combinations of drugs that reduce variability even more effectively than calcium channel blockers could greatly reduce the occurrence of stroke.²⁸ Evidence from recent studies suggests that BPV, whether measured during clinic visits or by ABPM, is predictive of stroke and other cardiovascular events, and that calcium channel blockers—and to a lesser extent thiazide diuretics—are superior to other drugs in reducing BPV and preventing stroke and other vascular events. The evidence also suggests that the older β -blocker atenolol, which increases BPV, should probably only be used as a first-line drug if there are other compelling clinical indications, such as ischemic heart disease. It should be stressed that there is no evidence one way or the other that the newer generation of β -blockers affect BPV.²

The recent introduction of what we have termed the “flexipill”—to distinguish it from its predecessor, the “polypill”—is a welcome therapeutic innovation.² The pharmaceutical industry has now recognized the need for flexible dose combinations within one tablet allowing a prescribing physician to in-

crease the dosage of the component parts in a single tablet according to BP response. In this regard, we now have flexipill combinations of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors with calcium channel blockers, angiotensin receptor blockers and angiotensin-converting enzyme inhibitors with thiazide diuretics, and β -blockers and renin inhibitors with thiazide diuretics. Triple-drug combinations with flexible dosage options are about to be introduced. Quite apart from the advantages of being able to

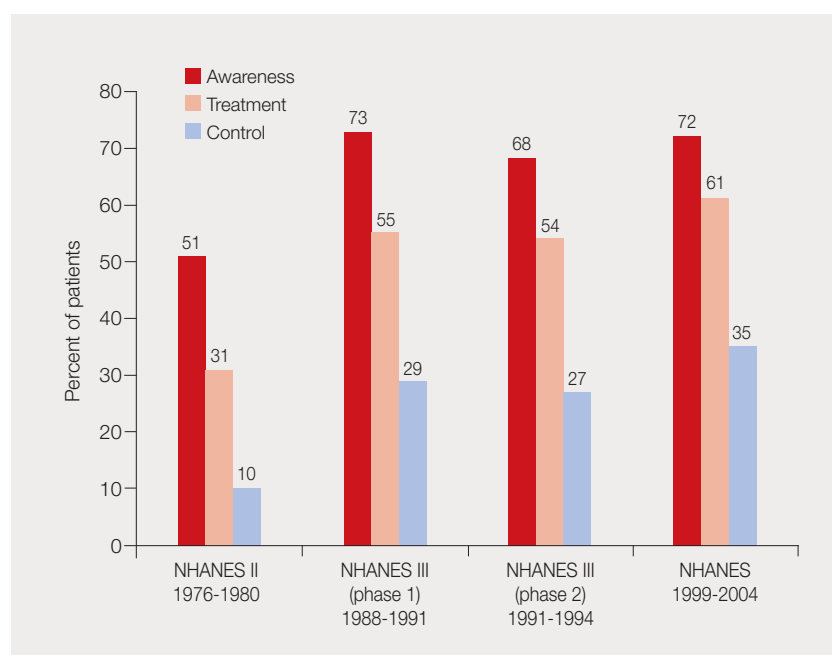


Figure 2. Rates of awareness, treatment, and control of high blood pressure in the United States (1976-2004).

High blood pressure is defined as a reading of 140/90 mm Hg or more for persons between the ages of 18 and 74 years. Despite major improvements in blood pressure therapies in recent years, some 28% of Americans with hypertension do not know they have the condition, 39% are receiving no therapy, and 65% have insufficient blood pressure control.

Abbreviation: NHANES, National Health and Nutrition Examination Survey.

Modified from reference 57: Chobanian. *N Engl J Med.* 2009;361:878-887. Copyright © 2009, Massachusetts Medical Society.

prescribe low doses of multiple drugs in one tablet—thereby minimizing the adverse effects that might occur with higher doses of the individual components—and the beneficial effects this should have on compliance, the flexipill provides a means of not only lowering BP, but of also reducing BPV by using medication with contrasting modes of action.

Recently, perindopril in combination with amlodipine has been shown to significantly reduce total and cardiovascular mortality as compared with atenolol/diuretic. A greater reduction in BPV, central BP, and specific vascular protective properties of perindopril (improvement in arterial stiffness and endothelial function) might explain these results.⁶²

The body of work highlighting the importance of BPV should focus the minds of clinical scientists, the pharmaceutical industry, those interested in BP measurement, and doctors who

care for patients with hypertension on the need to study the mechanisms of BPV, to devise methods for its accurate detection, and to determine how best to reduce it. Drugs that reduce BPV might be more beneficial than drugs that do not reduce BPV, and prerandomization (or pretreatment) run-in assessment to test for BPV could be informative.⁶³ Trials are also needed to determine if drugs and combinations of drugs that reduce both BP and BPV will have a beneficial effect on

outcome. It is likely that the duration of action and time of administration of drugs will be important considerations in reducing BPV. Detecting BPV appears straightforward in retrospective studies, but this is not readily done in practice. Improved methods of collecting and storing data electronically so as to detect trends in BP in the office and home, and the increased use and exploration of the indices of ABPM are strategies that should be examined.² ■

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STABILISATION DE LA VARIABILITÉ DE LA PRESSION ARTÉRIELLE : UNE NOUVELLE CIBLE THÉRAPEUTIQUE DANS L'HYPERTENSION

La variabilité de la pression artérielle (VPA), reconnue depuis de nombreuses années comme représentant un risque d'événements cardio-vasculaires, a récemment attiré l'attention du fait qu'un certain nombre d'études ont montré qu'une augmentation de la variabilité permet la prédictions d'événements cardio-vasculaires, et tout particulièrement les AVC, et que diverses classes de médicaments peuvent influencer sur la variabilité, soit de façon bénéfique, en la réduisant, soit de façon négative en l'augmentant. La littérature récente insiste sur l'importance de réduire le niveau de la pression artérielle moyenne, selon les recommandations de toutes les directives ; cependant, les médecins sont maintenant tenus de prendre en compte les médicaments, comme les inhibiteurs calciques, qui réduisent la VPA. Néanmoins, la prescription des médicaments, comme les anciens β -bloquants, qui augmentent la VPA, devrait toujours être étudiée soigneusement dans le contexte de l'état cardio-vasculaire global du patient. L'introduction récente de comprimés flexibles contenant une association de médicaments, comme l'amlopiline/périndopril, qui diminue à la fois la pression artérielle moyenne et la VPA permet au médecin d'obtenir les deux buts souhaités du traitement. La mesure de la VPA à court terme peut être facilement réalisée par la mesure de la PA en ambulatoire, contrairement à la mesure de la variabilité à long terme à chaque visite, dont la mesure ne va pas si facilement de soi en pratique courante.