The results of a number of studies performed over the years support the hypothesis that short-term blood pressure (BP) variability (BPV) assessed within 24 hours is an independent determinant of organ damage and cardiovascular events in hypertension.1,2 More recently, a few articles have raised interest also in BP fluctuations occurring over longer time periods. Rothwell et al3 assessed the variability in clinic BP or in average 24-hour ambulatory BP values occurring between visits. They analyzed previously collected data demonstrating an independent association of such visit-to-visit variability with (mainly) cerebrovascular events. The principal disadvantage of this approach, however, is its limited applicability in the daily management of hypertensive patients, where it is difficult to obtain BP data under a stable antihypertensive treatment regimen over a consistent number of visits. An alternative method, devoid of this difficulty, is to assess day-by-day BPV making use of home BP values obtained over several days. Its validity is supported by studies demonstrating the relationship of day-by-day BPV with cardiovascular outcomes.4

However, in spite of the data supporting the clinical relevance of BP fluctuations over time, a number of reasons have until now prevented the introduction of BPV assessment in daily clinical management of hypertension. Among them is the yet missing direct evidence in humans that a reduction in BPV by treatment provides cardiovascular protection beyond the ability to lower day-by-day BPV. Moreover, although animal studies suggested the possible beneficial role of calcium channel blockers (CCBs) in lowering BPV independent of changes in mean BP levels,5 longitudinal data in humans on the ability of antihypertensive drugs to reduce BPV independently from their effect on mean BP levels are still largely missing. A recent meta-analysis on the effects of different drug classes on visit-to-visit office BP variability can hardly be considered conclusive, because it was based on the retrospective assessment of interindividual rather than of intraindividual BP variability, a statistical approach of questionable validity.6

The article by Matsui et al7 published in the present issue of Hypertension provides an important contribution with regard to the effects of antihypertensive drugs on BPV. It reports the results of a post hoc analysis of Japan Combined Treatment With Olmesartan and a Calcium-Channel Blocker Versus Olmesartan and Diuretics Randomized Efficacy Study, where patients initially treated with an angiotensin antagonist (olmesartan) were randomly assigned to receive additionally either a CCB (azelnidipine) or a diuretic (hydrochlorothiazide). Changes in average home BP levels and in day-by-day home BPV were assessed after a 24-week follow-up. The main finding of this study is that the addition of azelnidipine to olmesartan led to a significantly larger reduction in day-by-day variability of BP (and also of heart rate) than the addition of hydrochlorothiazide, with similar reductions in mean BP in both groups. Moreover, the results suggest that this reduction was independently related to a reduction in aortic stiffness (assessed through carotid-femoral pulse wave velocity) in the azelnidipine group.

These results are stimulating from several points of view. One of them is the clinically interesting possibility that hypertensive patients with elevated day-by-day BPV might benefit from treatment with CCBs. Dedicated ad hoc longitudinal studies are now needed to further explore this possibility. Moreover, it would be essential to verify whether the ability to lower day-by-day BPV is a common feature of all CCBs or is restricted to the combination of an angiotensin receptor blocker with a particular CCB (in this case azelnidipine). Another important issue is the identification of the mechanisms responsible for day-by-day BPV and its changes by treatment. It is clear that BP variations assessed over different time periods may reflect the impact of very different physiological factors (Figure 1). Very short-term BP changes (over seconds or minutes) may reflect central and reflex autonomic modulation,8 as well as changes in arterial wall properties.1 BPV over 24 hours heavily depends also on a subject’s activity, including sleep-wakefulness cycle. Visit-to-visit variability may in turn be driven, among other factors, by changes in antihypertensive treatment, by the inconstant accuracy of office BP measurements, by the degree of patient therapeutic adherence, and by seasonal BP changes, either through the direct physiological effects of ambient temperature or through improper modifications of therapy in response to changing weather conditions.9 As an aside, these differences emphasize the need for a proper distinction between
spontaneous BPV and BP variations attributed to an imperfect stability of BP control, better reflected by visit-to-visit BP fluctuations. In such a context, day-by-day BP variability finds its position somewhere between 24-hour and visit-to-visit BPV. Home BP measurements, being performed in fairly standardized conditions, are mostly devoid of the influence of subject activity and, in this respect, home day-by-day BPV may be similar to visit-to-visit BPV. However, home BPV between days also shares some features with 24-hour BPV, insofar as the information on BP changes is collected over a relatively short time (several days), when both subject’s physiological characteristics and treatment regimen remain stable. Therefore, although some influence of patient adherence to prescribed treatment on day-by-day BPV is possible, the relevance of this factor in the context of the study by Matsui et al seems rather unlikely. Unfortunately the information on treatment adherence was not reported in this study,7 and, thus, it is not possible to completely rule out its contribution to the observed differences in BPV. The identification of mechanisms responsible for the effects of a given treatment on different measures of BPV is important to understand the origin of its possible benefits. In the study by Matsui et al, the reduction in day-by-day BPV was independently related to the reduction in carotid-femoral pulse wave velocity in the azelnidipine group. Although the relationship between BPV and arterial stiffness is a physiologically appealing possibility, this result should be interpreted cautiously. Indeed, although this relationship is easy to explain in the case of short-term BPV, it is not so clear how changes in BP between days might be related to changes in arterial wall properties. This interpretative difficulty is emphasized by the fact that, in the study by Matsui et al,7 the reported multivariate model explained merely 10% of variance in BPV reduction. Moreover, carotid-femoral pulse wave velocity change had borderline significance in this model, which suggests that the extent of its independent contribution to BPV reduction was very limited.

BPV response to CCB treatment might also depend on an improved efficacy of autonomic cardiovascular control mechanisms, specifically of baroreflex function, contributing to increased BP stability. This suggestion is supported by previous studies, which, however, were focused on short-term or very short-term BPV.10 Caution is needed, therefore, when trying to extrapolate their results to BP variations occurring between days. For instance, increased baroreflex sensitivity is physiologically accompanied by increased heart rate variability, whereas exactly the opposite occurred in the azelnidipine group of the study by Matsui et al.7 This finding supports the notion that cardiovascular variability assessed within 24 hours and that estimated on a day-by-day basis may represent 2 distinct phenomena with different physiological backgrounds.

Finally, some other aspects of the study by Matsui et al7 should be mentioned. The participants of the study were relatively old and with long-standing hypertension, leaner than typical hypertensive patients prevailing in Western populations and with a low percentage of smokers. This raises some doubts regarding the generalizability of the study results, and similar data obtained in different populations are, thus, needed to confirm the general value of these data. Moreover, the sample size was rather small, thereby inevitably reducing the power of exploratory analyses. Finally, the study design was not double blind and, therefore, some inherent bias may not be completely ruled out.7

Nevertheless, the study by Matsui et al7 provides a valuable contribution to the ongoing research on the clinical relevance of BPV. First, it offers further support to the usefulness of including the assessment of this parameter in everyday clinical practice. Second, it may allow for a better understanding of which therapies should be preferred to reduce an increased BPV in hypertension and the related risk increase. Finally, it may give some hints on the involved physiological and pathophysiological mechanisms, thus indicating future research directions in this interesting field.
Disclosures
None.

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