

## Prognostic Value of Long-Term Blood Pressure Variability The Evidence Is Growing

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For many years, interest in blood pressure (BP) variability has been limited to the BP variations that occur within a 24-hour period and make BP values often markedly different between and within different periods of the day and night. Evidence has been obtained that some of these variations (eg, the daily BP peaks and the morning BP rise) are independently related to organ damage and the risk of cardiovascular events.<sup>1,2</sup> Further, it has been shown that this is also the case for markers of overall BP variability, the values of which (that increase with mean BP and age<sup>3</sup>) are also related to organ damage and cardiovascular risk.<sup>4</sup> A recent example was provided by the data obtained in the general population of the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, in which 24-hour erratic BP variations (ie, the variations unexplained by the systematic BP oscillations induced by sleep and digestion) showed a positive relationship with the 12-year incidence of cardiovascular mortality, independently of the 24-hour mean BP values.<sup>5</sup>

For many years, the attention devoted to 24-hour BP variability has marginalized the interest in other types of BP variability, such as those occurring between days or months. On the descriptive side, evidence has been largely limited to the observation that there are clear-cut seasonal BP variations (ie, that BP is several mm Hg lower in summer than in winter)<sup>6</sup> that are attributable to, at least in part, the vasodilator effect of higher temperatures.<sup>7</sup> With regard to prognosis, the conclusion was drawn that long-term BP variations may have no clinical relevance, based on the Framingham observation that cardiovascular events did not have a relationship with BP lability (ie, the tendency of BP to differ between biannual data).<sup>8</sup> However, this has been challenged by studies conducted during the last several years that suggest that differences in BP values between monthly or yearly visits may have prognostic value. By retrospectively analyzing the results of the International Verapamil-Trandolapril Study (INVEST) trial on ≈23 000 hypertensive patients with a history of coronary disease, we showed that for a given mean in-treatment BP, the risk of cardiovascular morbidity and mortality, and that of stroke in particular, bore an inverse

relationship with the percentage of visits in which BP was reduced to <140/90 mm Hg (systolic/diastolic; <sup>9</sup> Figure 1). That is, the consistency of BP control between visits made patients less prone to cardiovascular events. This has been more recently given an elegant and more complete demonstration by Rothwell et al,<sup>10</sup> who have shown, via retrospective analysis of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and other trials on hypertensive patients, that the standard deviation or the variation coefficient of the average in-treatment BP, as obtained by visits performed throughout several years of treatment, represented an independent cardiovascular risk factor, again particularly for stroke. Indeed, the data of Rothwell et al,<sup>10</sup> suggested that the predictive value of between-visit BP variability is greater than that of average in-treatment BP.

The prognostic importance of between-visit BP variability receives additional support by the article of Muntner et al,<sup>11</sup> published in this issue of *Hypertension*, in which the risk of all-cause mortality was >50% greater in subjects in whom the standard deviation of the average of a 3-visit systolic BP was ≥4.8 mm Hg than in subjects in whom the standard deviation was less than this value. However, this is accompanied by additional findings. First, as emphasized by the authors, data were obtained in a general population (that of the National Health and Nutrition Examination Surveys) (NAHNES) rather than in the selected persons recruited for trials. Second, information was provided on factors that make between-visit BP variability greater, which turned out to be, such as for 24-hour BP variability,<sup>3</sup> age and BP; however, in addition to those factors, female gender, a history of myocardial infarction, diabetes, several measures (albuminuria, estimated glomerular filtration rate, and pulse pressure) of organ damage and cardiovascular risk factors. This may not be surprising because previous cardiovascular events, organ damage, and risk factors are associated with a derangement of mechanisms subserving BP homeostasis as well as with large and small artery structural damage that amplifies BP changes in response to environmental or central stimuli (and make measurable BP variations more likely). Finally, and of special interest, the relationship of between-visit BP variability with all-cause mortality was seen in a population in which BP was normal (systolic BP 125 mm Hg to 127 mm Hg), suggesting that visit-to-visit BP variability may have a prognostic value even when mean BP is far from being elevated. This was further supported by the results obtained after excluding from analysis subjects on antihypertensive drug treatment, which were similar to those obtained in the group as a whole.

The article of Muntner et al<sup>11</sup> also has several limitations that do not detract from the interest of the results but may

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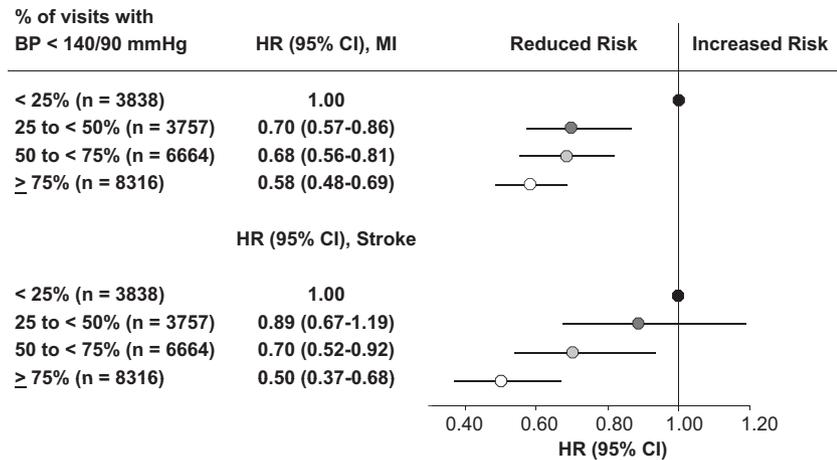
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(*Hypertension*. 2011;57:141-143.)

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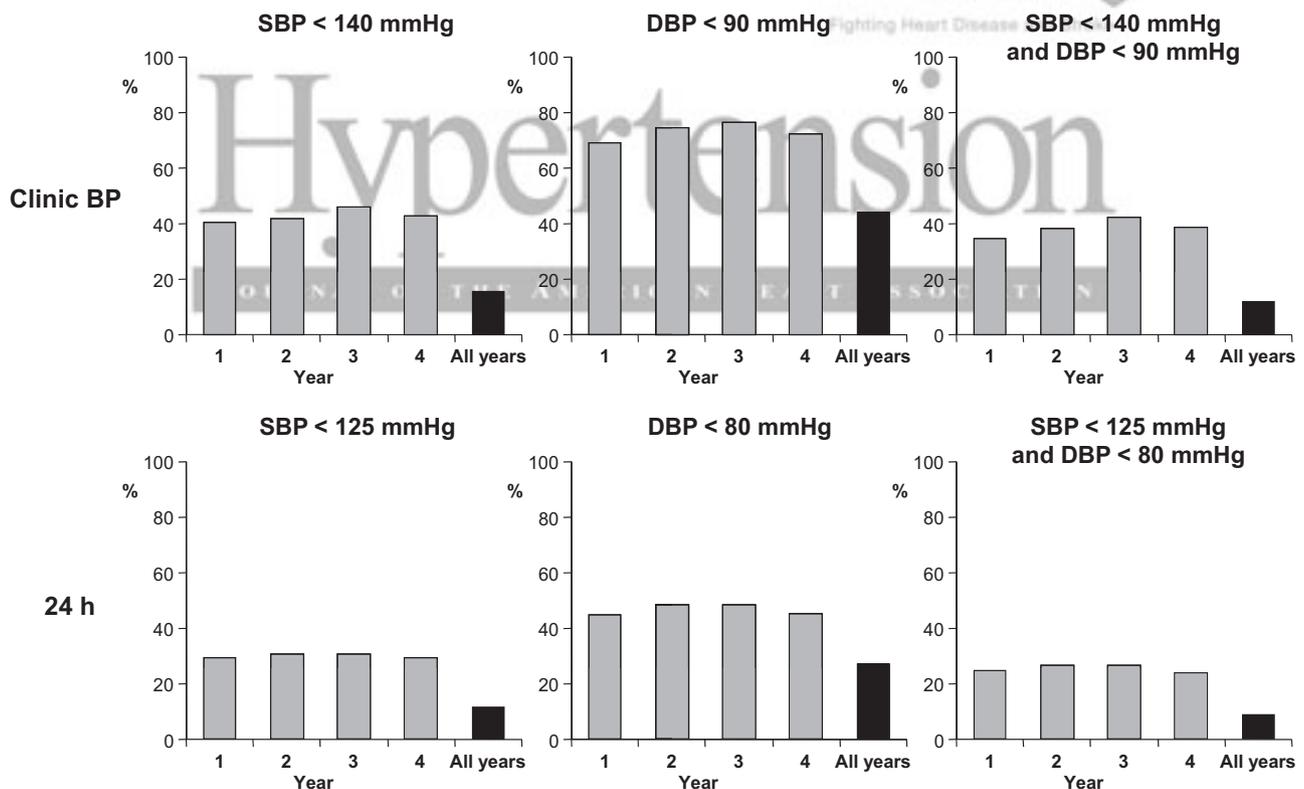
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DOI: 10.1161/HYPERTENSIONAHA.110.165852



**Figure 1.** Relative risk (hazard ratio [HR]) of myocardial infarction (MI) or stroke according to the percentage of visits with BP <140/90 mm Hg. The group in which this occurred in <25% of the visits was taken as reference. Data were adjusted for differences in baseline demographic data, BP, and cardiovascular risk factors as well as for in-treatment average BP.<sup>9</sup>

make collection of additional data desirable. First, the population studied was small (n=956), and during the otherwise commendable long (14-year) follow-up, there was no collection of BP data, which were only available at the study inception. Second, BP values were obtained from visiting patients at home as well as from asking them to come to a mobile examination center. This may have generated a higher between-visit BP variability because home BP is lower than clinic BP, at least when self-measurements are used.<sup>12</sup> Third, BP standard deviation was calculated from 3 values, which does not compare favorably with the larger number of values (≥7) available in previous studies<sup>10</sup> and may have limited the accuracy of the estimate. Finally, the visits were spaced by an

average period of only a few days, and the median time interval within which the visits in the mobile examination center were completed was 17 days. This is not in itself a limitation, but rather a difference from previous studies in which BP variability was calculated from visits performed at several-month intervals. Thus, the study of Muntner et al<sup>11</sup> may draw attention to day-to-day BP variability (ie, an intermediate temporal dimension between 24-hour and monthly or yearly BP variability). It should be emphasized that this intermediate BP variability may help the practicing physician to optimize antihypertensive treatment more than the long-term one because information can be collected quickly rather than after months or years, when the damage of



**Figure 2.** Rate of clinic and ambulatory systolic BP (SBP) and diastolic BP (DBP) control at each year and throughout the 4 years of treatment in the European Lacidipine Study on Atherosclerosis study. Clinic BP control was defined as an SBP/DBP value of <140/90 mm Hg, and 24-hour (24 h) BP control was defined as an SBP/DBP value of <125/80 mm Hg.<sup>13</sup>

inconsistent BP control has progressed and treatment modifications may come too late.

In conclusion, the study by Muntner et al<sup>11</sup> provides additional evidence that long-term BP variability is prognostically relevant, thus supporting the recommendation that treatment optimization also means avoidance of an inconsistent BP control as well as of large BP differences from one visit to another. Unfortunately, this is quite often the case. For example, in the European Lacidipine Study on Atherosclerosis (ELSA) study, only about one third of hypertensive patients had consistent clinic and ambulatory BP control over the 4-year treatment period, whereas in the remaining two thirds, BP was controlled at one visit but not at the following visits or vice versa (Figure 2).<sup>13</sup>

### Disclosures

None.

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*Hypertension*. published online January 3, 2011;

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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