One of the most interesting findings of hypertension research in the past 10 years has been that the cardiovascular protective effects of antihypertensive drugs depend not only on the mean blood pressure (BP) values achieved during treatment but also on the consistency of BP control between on-treatment visits. This was suggested in 2007 by the observation that in patients with hypertension and coronary disease, the protective effect of antihypertensive drugs increased because the percentage of on-treatment visits in which BP was reduced to <140/90 mmHg increased, even when data were adjusted for the average BP achieved throughout the treatment period. It was documented on a more precise numeric basis in 2010 by the observation that, in hypertensive patients at high cardiovascular risk, the risk of stroke and, to a lesser extent, coronary events increased because visit-to-visit BP variability increased. Similar findings have since been obtained in studies on patients with diabetes mellitus, chronic renal damage, and other diseases, which have also shown that visit-to-visit BP variability may impact not only on major cardiovascular events but also on other types of outcomes, including alterations of kidney function and cognitive decline. Although few discordant data have also been reported, this has led to the currently accepted concept that, to maximize cardiovascular protection, BP control needs to be as much as possible steady over time. This implies that physicians should not consider absence of BP control at single visits as of marginal clinical importance (and thus indulge in therapeutic inertia) because this may reduce patients’ chance of survival free of diseases.

The studies that have addressed visit-to-visit BP variability are unfortunately also characterized by limitations. One, this phenomenon has to date only be analyzed post hoc, which means that data have been derived from nonrandomized group comparisons, with thus the possibility for the results to be determined by baseline between-group differences, rather than to on-treatment differences of visit-to-visit BP variability. Two, visit-to-visit BP variability has commonly been assessed by the SD or other measures that are not entirely independent on mean BP values, whose contribution to the results can thus not be unequivocally excluded. This has led to the effort to modify the SD until a value unrelated to the mean is found, an empirically based procedure that is not devoid of inconveniences and criticism. Finally, an important limitation has always been regarded to be the paucity of information on the mechanisms leading to visit-to-visit BP variations. The hypothesis has been advanced that, as for 24-hour or short-term BP variability, these variations are accounted for by spontaneous (and thus largely erratic) modifications of the factors influencing regional circulations and BP values, such as arterial distensibility, sympathetic tone, release of vasoactive substances, myogenic reactivity, baroreflex sensitivity, etc. Modifications of the alerting response to the physician’s or nurse’s visit may also be involved, however, together with more trivial factors such as the greater or lesser temporal distance of the BP measurements from the assumption of antihypertensive drugs at different visits.

In the above context, the possibility has progressively gained ground that visit-to-visit BP variability might depend on the greater or lesser adherence of the patient to the treatment regimen because of the growing evidence that adherence to treatment (1) differs markedly among patients with hypertension; (2) shows pronounced time-related variations also within patients; and (3) bears a close relationship with patients’ outcome in both sexes, at all ages and with most, if not all, antihypertensive drug treatments. Expanding previous evidence by the same group, the article published by Kronish et al on this issue of Hypertension provides evidence that adherence to antihypertensive drug treatment is indeed involved in the determination of visit-to-visit BP variability. The authors made use of the data collected in the hypertensive patients of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) to obtain a large group (n=16,878) in which adherence was ≥80% of all prescribed medicaments, and a smaller one (n=2,912) in which it was below this figure. During the trial duration, patients showing a lower adherence exhibited a visit-to-visit BP variability that was modestly but significantly greater than that seen in patients with a better adherence (systolic: +8.5%; diastolic: +9.6%; P<0.001 for both). The difference remained significant after multivariable adjustment, although extending the adjustment to the adherence data did not eliminate the observed association between visit-to-visit BP variability and cardiovascular outcomes. This led the authors to also conclude that visit-to-visit BP variations owe their adverse prognostic significance not only to the varying level of adherence to treatment but also to other factors.
The demonstration that adherence to treatment contributes to the magnitude of visit-to-visit BP variability sheds light into the black box that has to date characterized the mechanistic aspects of this phenomenon. The study of Kronish et al., however, has several limitations that, although acknowledged and discussed by the authors, have to be kept in mind in order for the results to be seen in perspective and for future studies to try to adopt improved designs and procedures. One limitation is that adherence to treatment was quantified by patient self-reporting, that is, a method that is regarded as the most inaccurate among those by which adherence is assessed in research and clinical practice. The authors devoted a substantial part of the discussion to this problem, arguing that self-reporting of adherence to treatment has been shown to correlate with other measures of adherence. Furthermore, they engaged in many sensitivity analyses that did not disprove the results of the initial one and make the conclusion that adherence plays a role in the determination of visit-to-visit BP variability scientifically acceptable. Yet, in a previous investigation by some of the authors of the present study on a cohort of >2000 patients followed for 4 years, it was observed that low, medium, and high levels of adherence to antihypertensive medications as quantified by self-reporting did not relate to the risk of cardiovascular outcomes, at variance from another measure of adherence such as the medication possession ratio. It will thus be desirable for future studies to further address this issue by the adoption of objective measures of adherence that more consistently reflect the changes of cardiovascular risk induced by treatment. It will also be desirable to assess adherence in a fashion that takes into account the dynamic nature of this phenomenon. In this study, adherence was assessed by ≥2 visits during the 2- to 28-month period that followed randomization to treatment, which means that although in some patients repeated information was available, in others adherence was defined from an occasional report only. We know, however, that how patients comply with the prescribed treatment regimen can hardly be defined in this way because adherence to the prescribed drug(s) can be highly variable over time. Taking an extreme example treatment discontinuation for more or less prolonged periods may coexist in a given individual with full adherence to treatment in other periods.

A second limitation is the trial context on which the study was based. Using data that are collected in trials carries the advantage that identification of the outcomes is usually more accurate than that provided by observational studies or other data sources. It has the disadvantage, however, that in randomized trials patients’ high motivation and close follow-up make overall adherence uncharacteristically high. In this study, only <15% of the patients reported a lower than 80% use of the medicaments which (1) made the numeric between-group comparisons unbalanced and (2) did not allow to explore the effect of lower adherence levels (so common in real-life antihypertensive treatment) on the relationship between visit-to-visit BP variability and outcomes. This is an important issue to address because adherence to treatment has often been shown to markedly improve cardiovascular protection already when it raises to intermediate levels (50% to 75% of the available drugs), with little further advantage when the level increases further.

The third limitation originates from the previous ones. Because of the limited accuracy and extent of the adherence to treatment measures, adjustment for adherence to rule out its contribution to the adverse prognostic role of visit-to-visit BP variability has inevitably a limited value. This weakens the second conclusion of the article, that is, that other factors involved in the determination of BP variability contribute to their adverse prognostic value. This may well be the case, but it is up to future studies in which adherence to treatment will be measured accurately within its usual wide range to move ahead from the present contribution and to confirm what seems at this stage just an interesting suggestion.

Disclosures

None.

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Visit-to-Visit Blood Pressure Variability: An Insight Into the Mechanisms
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