Effective drug treatment of hypertension for the prevention of fatal and nonfatal cardiovascular disease passed its 50th anniversary 2 years ago. Until recently, the most consistent observation among trials had been that stroke risk was directly related to the fall in blood pressure on treatment. Older trials established the value of antihypertensive drug treatment and generally recruited disease-free participants at their outset. Recent trials have focused on less healthy participants. Recruitment has been extended to those with a prior stroke, recent myocardial infarction, coronary artery disease, chronic renal disease (with or without diabetes mellitus), heart failure, and combined high-risk states and the elderly (old-old). The benefit of antihypertensive drug treatment is still related to the reduction in blood pressure. Differences between drug classes have been found in some but not all trials; the differences are generally small, even if statistically significant. Antihypertensive drug treatment is effective in reducing risk for those with a higher disease burden, but risk is never lowered to levels equal to those who have lower pressure without antihypertensive drug treatment and lack prior cardiovascular disease. The hands of the cardiovascular clock may slow, but they never stop or reverse. It is a challenge to unmask traits that might account for the limited effectiveness of antihypertensive drug treatment in its present form.

In a retrospective look at blood pressure patterns in several stroke trials and the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering (ASCOT BP) trial, Rothwell and colleagues examined whether intervisit variability and episodic peaks in pressure had clinical significance independently of usual blood pressure. They found a striking effect with the top 3 deciles of systolic pressure variability (defined as the standard deviation for visit pressures) having hazard ratios in the range of 3 to 8 for subsequent stroke. In a larger meta-analysis, interindividual variation in pressure was linked to drug class and to outcome. Calcium channel blockers were associated with less variability and better outcomes, whereas β-blockers were associated with the opposite. Variability defined for ambulatory blood pressure monitoring (within-day) had far less association with outcome. However, increased day-to-day variability in home systolic blood pressure monitoring has been associated with increased cardiovascular and stroke mortality but not with cardiac mortality.

In this issue of Circulation, Mancia et al continue their retrospective look at the European Lacidipine Study on Atherosclerosis (ELSA), which compared a β-blocker, atenolol, with a calcium blocker, lacidipine, in a randomized clinical trial. ELSA enrolled middle-aged hypertensives with an average age of 56 years; 33% had the metabolic syndrome, 5.5% were diabetic, and only 2.4% had a history of significant cardiovascular disease. The primary outcome was the surrogate, carotid-intimal thickness. Cardiovascular events (stroke, myocardial infarction, and cardiovascular death) were also evaluated. Both intervisit and 24-hour ambulatory blood pressure variability were assessed. On-treatment clinic and 24-hour systolic blood pressures were correlated with cardiovascular events with no difference between the 2 drugs. Lacidipine was associated with less progression of carotid-intimal thickening compared with the β-blocker. Neither intervisit nor ambulatory blood pressure monitoring variability differed between the 2 groups, and neither was related to progressive carotid-intimal thickness or to cardiovascular outcomes. What accounts for the differences between ELSA and the previous reports?

ELSA recruited a predominantly disease-free cohort. The duration of ELSA was shorter and the event rate for stroke and other cardiovascular events was much less than in the other trials. These factors might account for differences related to blood pressure variability. However, the methods used might also be relevant. Table 1 summarizes similarities and differences in clinic measurement, ambulatory blood pressure monitoring, and home blood pressure monitoring. Ambulatory blood pressure monitoring provides abundant data for a single day. Home

### Table 1. Comparison of Methods for Clinical Measurement of Blood Pressure

<table>
<thead>
<tr>
<th>Method for Blood Pressure</th>
<th>Characteristics</th>
<th>Sources of Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic measurement</td>
<td>Intervisit variation; small sample size, long intervals</td>
<td>Diet, weight change, adherence to medication, anxiety because of visit, other</td>
</tr>
<tr>
<td>Ambulatory monitoring for 24 h</td>
<td>Interhour variation; large sample size, limited to 24–48 h, includes day-night for intra-individual patterns</td>
<td>Activity, awake, asleep, other behavior, pharmacodynamics (peak-trough)</td>
</tr>
<tr>
<td>Home monitoring</td>
<td>Intercity variation; sample size varies, intervals vary from days to weeks to months</td>
<td>Work, nonwork, adherence to medication, other</td>
</tr>
</tbody>
</table>

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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pressure monitoring conveys interday, week, or month measurements. The clinic method discloses few measurements taken over long time intervals and apart from ordinary life. If intervisit or interday variability for blood pressure is a robust predictor for cardiovascular outcomes, 1 feature stands out that differs from ambulatory blood pressure monitoring. That feature is patient adherence. When degree of control of hypertension in relation to outcomes in the International Verapamil SR–Trandolapril Study (INVEST) trial was examined, those with the highest percentage of visits in which pressure was controlled had the lowest event rates and the lower on-treatment pressures. A similar pattern was found in a look back at the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). An example of how on-treatment pressures might affect average pressure, percent control, and variability is shown in Table 2. Those who attend visits probably also take their medication (outside of research studies in which medication is provided) and fill and refill their prescriptions. Erratic adherence in high-risk populations for which sustained control of hypertension is most needed may well lead to greater differences for intervisit pressures (increased variability) and worse outcomes. It is likely, but not adequately studied, that adherence is greater in clinical trials than in usual clinical practice. Younger age, use of multiple drugs, drug classification, male sex, and duration of treatment >6 months are associated with lower adherence. In comparing drug classes, Kronish et al found that adherence to β-blockers and diuretics was less than for calcium blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Perhaps the apparent superiority for calcium blockers in the prevention of stroke and in lower blood pressure variability is linked to better adherence.

Differences in adherence to medication may not account entirely for the increased intervisit variability of systolic pressure and greater risk in vulnerable populations. It is too easy to simply blame the patient. Loss of normal physiological control of blood pressure with aging leads to asymptomatic orthostatic hypotension and its added risk for stroke and cardiovascular disease. Small differences in position or clinic conditions might cause greater differences in pressures. It is likely, but not adequately studied, that adherence is greater in clinical trials than in usual clinical practice. Younger age, use of multiple drugs, drug classification, male sex, and duration of treatment >6 months are associated with lower adherence. In comparing drug classes, Kronish et al found that adherence to β-blockers and diuretics was less than for calcium blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Perhaps the apparent superiority for calcium blockers in the prevention of stroke and in lower blood pressure variability is linked to better adherence.

What justifies a closer look at blood pressure variability for the current prevention of cardiovascular disease in high-risk groups? With electronic medical records available, blood pressures over several visits can easily be analyzed for average and variability. One such study indicates that visit-to-visit variability is not entirely random over several years. Norms can be established, but what then? Should antihypertensive medication be changed to reduce variability? What diagnostic steps should be taken for high variability? Should high variability trigger initiatives to change medication or to improve adherence? For now, pragmatic strategies require additional understanding of the mechanisms and pathology that underlie blood pressure variability. Without that knowledge, management of hypertension should remain based on the reduction of average blood pressure to desirable levels.

**Disclosures**

None.

**References**


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