Fluctuation: Does Blood Pressure Variability Matter?

Running title: Krakoff; Does blood pressure variability matter?

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Effective drug treatment of hypertension for prevention of fatal and non-fatal cardiovascular disease passed its 50th anniversary two 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 anti-hypertensive drug treatment (AHT) 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), heart failure, combined high-risk states and the elderly (old-old). The benefit of AHT is still related to the reduction in blood pressure. Differences between drug classes for have been found in some, but not all trials; the differences are generally small, even if statistically significant. AHT 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 AHT and lack prior cardiovascular disease. The hands of the cardiovascular clock may slow, but never stop or reverse. It is a challenge to unmask traits that might account for the limited effectiveness of AHT in its present form.

In a retrospective look at blood pressure patterns in several stroke trials and the ASCOT BP trial, Rothwell and colleagues examined whether inter-visit variability and episodic peaks in pressure had clinical significance independent 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 3-8 for subsequent stroke. In a larger meta-analysis, inter-individual variation in pressure was linked to drug class and to outcome. Calcium channel blockers were associated with less variability and better outcomes while beta-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 ELSA which compared a beta 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 (CIT). Cardiovascular events (stroke, myocardial infarction and cardiovascular death) were also evaluated. Both inter-visit and 24 hour ambulatory blood pressure variability were assessed. On-treatment clinic and 24 hour systolic blood pressures were correlated with cardiovascular events without difference between the two drugs. Lacidipine was associated with less progression of carotid intimal thickening compared to the beta blocker. Neither inter-visit nor ABPM variability differed between the two groups and neither were related to progressive CIT or to cardiovascular outcomes. What accounts for the differences between ELSA and the previous reports?

ELSA predominatly recruited a disease free cohort. ELSA’s duration was shorter and the event rate for stroke and other cardiovascular events was much less than the others. 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 for clinic measurement, ambulatory blood pressure monitoring and home blood pressure monitoring. Ambulatory blood pressure monitoring provides abundant data for a single day. Home pressure monitoring conveys inter-day, week or month measurements. The clinic method discloses few measurements taken
over long time intervals and apart from ordinary life. If inter-visit or inter-day variability for blood pressure is a robust predictor for cardiovascular outcomes, one feature stands out that differs from ABPM. That feature is patient adherence. When degree of control of hypertension in relation to outcomes in the 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\(^\text{12}\). A similar pattern has been found in a look-back at the ONTARGET trial\(^\text{13}\). 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 (and outside of research studies in which medication is provided) also 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 inter-visit pressures (increased variability) and worse outcomes. It is likely, but not adequately studied, that adherence is greater in clinical trials than in usual clinic practice. Younger age, multiple drugs use, drug classification, male gender, and duration of treatment more than 6 months are associated with lower adherence\(^\text{14,15}\). In comparing drug classes, Kronish found that adherence to beta blockers and diuretics was less than for calcium blockers, ACE inhibitors or angiotensin receptor blockers\(^\text{15}\). Perhaps the apparent superiority for calcium blockers in prevention of stroke and lower blood pressure variability\(^\text{5}\) is linked to better adherence.

Differences in adherence to medication may not entirely account for increased inter-visit variability of systolic pressure and greater risk in vulnerable populations. It’s too easy to simply blame the patient. Loss of normal physiologic control of blood pressure with aging leads to asymptomatic orthostatic hypotension and its added risk for stroke and cardiovascular disease\(^\text{16,17}\). Small differences in position or clinic conditions might cause greater differences in
pressure between visits in the elderly compared to younger and healthier participants. Older and less well patients often take other drugs, such as anti-depressants that might alter inter-visit pressures. Those with advanced carotid stenosis exhibit greater blood pressure variability by ambulatory blood pressure monitoring. More research is needed to define the specific characteristics that account for blood pressure variability in the increasing number of treated hypertensives.

What justifies a closer look at blood pressure variability for current prevention of cardiovascular disease in high risk groups? With electronic medical records available, blood pressures over several visits can be easily 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 anti-hypertensive medication be changed to reduce variability? What diagnostic steps should be taken for high variability? Should high variability trigger initiatives to change medication or 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 reduction of average blood pressure to desirable levels.

Conflict of Interest Disclosures: None.

References:

1. Veterans Administration Cooperative Study Group on Antihypertensive Agents, Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA. 1970;213:1143-1152.


1736.


**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>Inter-visit variation. Small sample size, long intervals</td>
<td>Diet, weight change, adherence to medication, Anxiety of visit, other activity, awake, asleep, other behavior, pharmacodynamics (peak-trough)</td>
</tr>
<tr>
<td>Ambulatory Monitoring 24 hours</td>
<td>Inter-hour variation. Large sample size, limited to 24-48 hours, includes day-night for intra-individual patterns.</td>
<td></td>
</tr>
<tr>
<td>Home Monitoring</td>
<td>Inter-day variation. Sample size varies, varying intervals from days to weeks to months.</td>
<td>Work, Non-work, Adherence to medication, other</td>
</tr>
</tbody>
</table>

**Table 2.** Example of clinic blood pressures and variability for two participants.

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 SBP</th>
<th>Visit 2 SBP</th>
<th>Visit 3 SBP</th>
<th>Visit 4 SBP</th>
<th>Average SBP</th>
<th>% Control</th>
<th>SD</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betty Steady</td>
<td>139</td>
<td>138</td>
<td>142</td>
<td>136</td>
<td>138.8</td>
<td>75</td>
<td>2.5</td>
<td>1.8%</td>
</tr>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eddy Erratic</td>
<td>142</td>
<td>130</td>
<td>141</td>
<td>135</td>
<td>137.0</td>
<td>50</td>
<td>5.6</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

Systolic blood pressures (SBP in mm Hg) are shown with average SBP’s, % control, SD and CV. The average pressure for Patient 1 is higher than for Patient 2, but variability is >50% lower for Patient 1, compared to Patient 2.
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