PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

Long-term visit-to-visit systolic blood pressure variability is more important than average systolic pressure in predicting cardiovascular outcomes: evidence from the Anglo-Scandinavian Cardiac Outcome Trial

PETER SEVER

National Heart and Lung Institute, Imperial College London, UK

In hypertensive patients, decisions on thresholds for treatment and target blood pressures have traditionally been derived from observational studies and randomised controlled trials of drug treatment. There is overwhelming evidence from the observational studies that the higher the blood pressure the greater the risk,[1] but it is important to point out that at most levels of blood pressure, age is a more important determinant of risk than the level of blood pressure.

It has been widely accepted, based on the results of many individual intervention trials, that the lower the achieved blood pressure, the better the cardiovascular outcome. However, pooled analyses of the trial data raise interesting questions as to whether, indeed, this is always true. From the Blood Pressure Lowering Treatment Trialists Collaboration,[2] this relationship appears to hold for stroke, but for other outcomes including coronary heart disease and total cardiovascular events, larger reductions in achieved blood pressure are not always associated with better outcomes. Moreover, the relationship is strongly influenced by the presence in these trials of subjects with type 2 diabetes, and when these patients are removed from the analyses, the relationship between blood pressure and outcome is much less clear[3]. Perhaps therefore, there are other blood pressure related features that are more important determinants of cardiovascular outcomes.

In 1994, Mancia and colleagues reported that the variability of blood pressure on ambulatory blood pressure recordings predicted target organ damage over a follow-up period of 7.5 years.[4] Shortly thereafter, Otsuka and colleagues, in 1997, reported that circadian amplitude of blood pressure was an important predictor of ischaemic stroke and nephropathy over a follow-up period of 6 years.[5] Thereafter, there were several studies reported from Japan,[6,7,8] showing that variability in office blood pressures predicted cardiovascular events and mortality. Stevens and colleagues have reviewed this important subject and published a meta-analyses of studies of both short-term and long-term blood pressure variability.[9]

The significance of these observations has been largely ignored and long-term visit-to-visit blood pressure variability has been considered an obstacle for the reliable estimation of usual blood pressure and considered as “background noise”. Moreover, clinical guidelines do not recommend treatment for blood pressure variability.

Having been influenced by Rothwell's observations on a cohort of patients presenting with a transient ischaemic attack, that the risk of subsequent stroke was strongly determined, not by mean blood pressure, but by long-term visit-to-visit variability,[10] we collaborated to review the database derived from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in order to test the hypothesis that long-term visit-to-visit blood pressure variability was a more important determinant of cardiovascular outcome than the mean blood pressure achieved during the trial.[10]

ASCOT was a randomised controlled trial in hypertensive subjects, comparing two different treatment strategies, atenolol +/- bendroflumethiazide and amlodipine +/- perindopril.[11] Mean blood pressures were well controlled during the trial following randomisation, but there were small differences in achieved blood pressure in favour of the amlodipine-based treatment by, on average, 2.7/1.4 mmHg. Preliminary analyses suggested that these small differences in blood pressure did not account for differences in cardiovascular outcomes,[12] which were in favour of the amlodipine-based treatment regimen for most cardiovascular outcomes, including mortality. We subsequently re-analysed the database, which included almost one million measurements of blood pressure throughout the 5.5 year follow-up period, and showed that in-trial mean blood pressure was a very poor determinant of cardiovascular outcomes.[10] There was no relationship between in-trial systolic blood pressure and coronary outcomes and only at the highest decile of in-trial systolic pressure was there any association with stroke (Figure 1). On the other hand, when outcomes were related to visit-to-visit systolic blood pressure variability throughout the trial (standard deviation, coefficient of variation of systolic pressure or variation independent of the mean), there was a strong and robust relationship between higher systolic variability and both stroke and coronary outcomes. Moreover, it was clear that there were substantial differences in the treatment effects on long-term blood pressure variability, with a gradual reduction throughout the trial with the amlodipine-based treatment regimen, contrasting with an initial rise in variability as participants were randomized to atenolol and, thereafter, as the trial progressed, a gradual fall presumably due to the introduction of second and third line drugs.[13] Further analyses provided robust evidence that long-term visit-to-visit variability and not achieved mean blood pressure, was the major determinant of the benefit in trial outcomes in favour of amlodipine-based treatment.

Subsequent to the publication of our findings, a number of other trials reported similar observations on the importance of long-term visit-to-visit variability, including ALLHAT,[14] the ADVANCE trial[15] and the African-American trial in subjects with chronic kidney disease[16]. Also, a review and meta-analysis has been published.[9]

At the end of the blood pressure-lowering arm of ASCOT, after 5.5 years follow-up, participants in the United Kingdom were flagged with the Office of National Statistics (subsequently NHS Digital), whereby data on hospitalisations and mortality, could be recorded over the following 15+ years of observation. Outcomes on mortality were derived from death certificates and non-fatal outcomes from electronic records which were classified using conventional ICD codes.

There were initially over 8,500 subjects from England, Wales and Scotland recruited into this ASCOT Legacy cohort, and over the total observation period, almost 5,000 cardiovascular events, including approximately 3,000 coronary events and 1,000 strokes were recorded. In the analyses of these data, which have recently been reported at the ISH meeting in Kyoto 2022,[17] there was a strong positive correlation between long term cardiovascular outcomes and in-trial systolic blood pressure variability adjusted for mean systolic pressure. There was a 20-25% increase in risk for each standard deviation increase in the standard deviation of systolic blood pressure. The importance of these observations is that the relationship with long-term visit-to-visit variability was independent of any differences in in-trial blood pressure as we had previously shown during the original trial. Further analyses (Figure 2), show very clearly that at all levels of systolic blood pressure, higher visit-to-visit systolic blood pressure variability confers a far greater risk. And, importantly, even in those who achieved blood pressures well within the normal range, higher levels of systolic blood pressure conferred substantial additional cardiovascular risk. However, these subjects,

according to contemporary guidelines, would not be considered for any further treatment. We have also reported that visit-to-visit variability is a far more important determinant of renal outcomes (development of chronic renal disease, renal failure and the need for renal replacement therapy), than in-trial mean systolic blood pressure.[17] In these 20-year observations, we also demonstrated that the benefits of the amlodipine-based treatment compared with atenolol-based treatment regimen on cardiovascular events, persisted despite the fact that there had been considerable cross-over of treatments in the post- trial period.

We conclude therefore:

1. That long term visit-to-visit systolic blood pressure variability is a major predictor of cardiovascular and renal events independent of mean systolic blood pressure.

2. That in many individual trials and meta-analyses, mean blood pressures poorly predict outcome.

3. In the long-term follow-up of ASCOT, participants formerly assigned the amlodipine-based treatment demonstrated a persistent reduction in cardiovascular events compared with those assigned atenolol-base treatment.

4. That in a review of antihypertensive drug classes only long-acting calcium channel blockers and, to a lesser extent, diuretics, reduce long-term visit-to-visit blood pressure variability.

5. That the effect of long-acting calcium channel blockers on blood pressure variability is a likely explanation for their long-term outcome benefits compared with other drugs on cardiovascular outcomes in major clinical trials.

6. That the implications of these findings for guidelines on blood pressure management have yet to be established.

Figure 1. Cardiovascular outcomes from ASCOT expressed as hazard ratios for deciles of increasing systolic blood pressure (upper panel) and visit-to-visit systolic blood pressure variability (lower panel).10 For systolic pressure only the tenth decile is significant for stroke outcome (red circle)

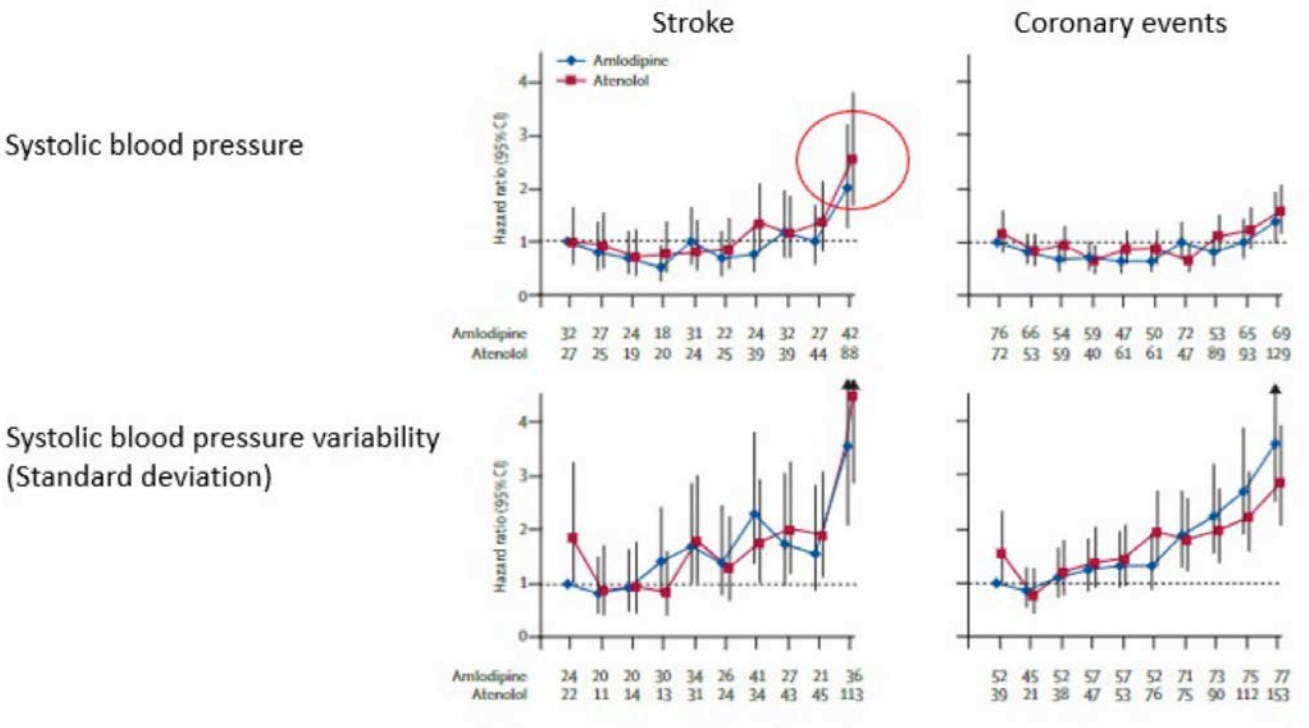
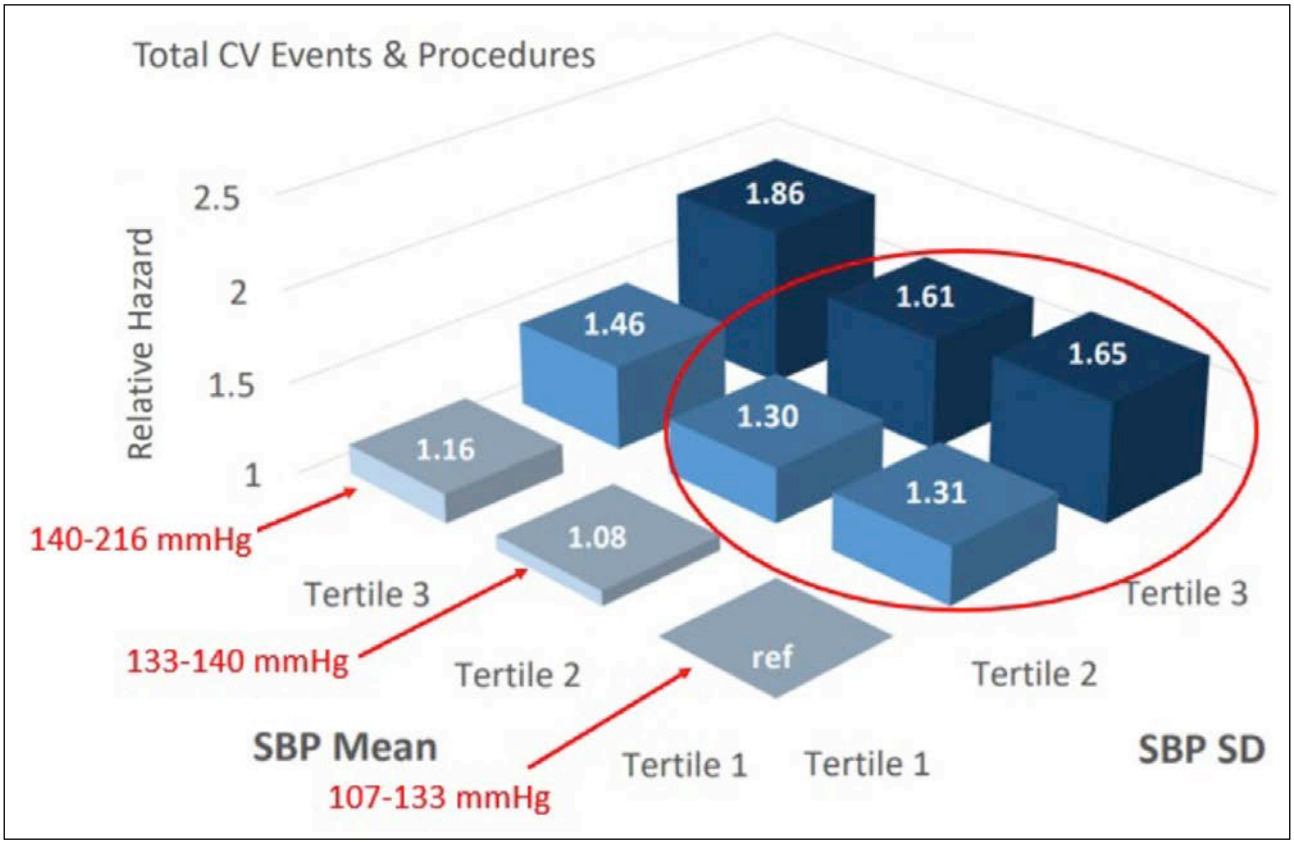


Figure 2. Total cardiovascular events in the 20 year ASCOT Legacy Programme shown by tertiles of systolic blood pressure and tertiles of systolic blood pressure variability (standard deviation SD). Ranges of systolic blood pressure are shown for each tertile. The red circle highlights participants for whom, according to guidelines, no further treatment is advocated. The data are based on almost 1 million measurements of SBP and approximately 5000 cardiovascular events.



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Peter Sever - p.sever@imperial.ac.uk