Wars, War Games, and Dead Bodies on the Battlefield
Variations on the Theme of Blood Pressure Variability

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See related article, pages 2860–2865.

Antihypertensive treatment is accepted as the most effective means for preventing stroke, and its effectiveness is solidly founded on a series of large randomized controlled trials. Hypertension experts can be proud that antihypertensive therapy has been the first among cardiovascular therapies that has been tested by randomized controlled trials using so-called hard end points (ie, fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, cardiovascular death, and death by any cause), all verified by independent blind clinical event committees.

Trials are intended to be examples of treatment in everyday life, and hard end point trials measure and compare results (or outcomes) of different interventions by simply counting dead bodies or wounded bodies on the battlefield. This is what is rightly considered solid evidence. Although trials generally cannot explore mechanisms, unavoidably (and, up to a given extent, usefully), investigators try to understand, and more often to figure out, the reasons and the mechanisms that may have led to differences in the measured outcomes. The same is the case in history: there is no uncertainty in the outcome of the battle of Waterloo, but historians take delight in interpreting (post hoc) the reasons and may conclude that Napoleon matched Wellington alone but lost to the combination Wellington plus Blücher, whereas Grouchy arrived too late to make a successful combination with Napoleon. Subtler interpretations may call on Napoleon’s bad health, on excessive raining, and the lot of mud that hampered the advantage of the French army, quick movement of troops, and the like. However, these exercises look like war games rather than real wars.

Like the outcomes of Napoleon’s wars, the benefits of antihypertensive therapy shown by randomized controlled trials have also stimulated post hoc interpretations and debates about the hypothesis that all benefit is caused by blood pressure-lowering or the alternative hypothesis that part of the benefit may be due to specific properties of some class of drugs. The favorable outcome of placebo-controlled trials that have used different drug classes as an active regimen strongly supports the interpretation of the preponderant role of blood pressure reduction. Furthermore, a host of more recent trials that have compared 2 different active regimens intended to achieve similar blood pressure can also be interpreted to confirm the predominant role of blood pressures reduction (similar outcomes with the 2 compared regimens when achieved blood pressures are similar). However, the few trials in which different rates of outcomes occurred despite no or little blood pressure difference have allowed the few adepts of blood pressure-independent benefits of some agents to maintain their faith alive.

If consensus about the paramount role of blood pressure reduction is overwhelming, there is more uncertainty about what blood pressure reduction is most relevant. Is it systolic or diastolic or pulse pressure, is it peripheral or central pressure, and is it office or out-of-office (ambulatory or home) blood pressure reduction? Furthermore, to predict outcomes of intervention, should we use the average of all values preceding the event or only the values closest to the event? In the greatest part of interpretative analyses, the mean of all blood pressures measured during treatment has been used, but the issue has not been exhaustively investigated.

Against this overwhelming background of commonly shared opinion about the predictive role of average on-treatment blood pressure, Rothwell and his associates have recently called attention to the additive or alternative role of variability of blood pressure during treatment. This has been a welcomed challenge to common opinion, because common opinion does not necessarily mean a correct opinion.

Rothwell and his associates propose 2 new measures of “variability”: (1) intra-individual visit-to-visit variability, that is, variability of an individual’s blood pressure from visit to visit; and (2) inter-individual variability, measured as the variability (the SD, variance, or coefficient of variation) of blood pressure in a group of patients on a given antihypertensive treatment. The 2 variability measures, when applied to large intervention trials, appear to predict incidence of stroke to a much greater extent than average blood pressure. Furthermore, in outcome trials comparing 2 antihypertensive regimens based on different drugs, the regimen associated with lower intra-individual or inter-individual variabilities was also associated with a lower incidence of stroke.

In an interesting article published in this issue of Stroke, Webb and Rothwell go even further and apply the calculation of inter-individual variabilities to a number of small (an average of 100 individuals per study), short-lasting (mostly <26 weeks) studies comparing different doses or different combinations of antihypertensive agents, studies in which the primary end point was the blood pressure change, and
obviously stroke or cardiovascular events could not be recorded. Nonetheless, the conclusion of the authors is that because of its low interindividual variability, “use of a high-dose of a calcium channel blocker alone or in combination with other agents is likely to be particularly effective in prevention of stroke.”

These far-reaching conclusions should be seen with the greatest interest but also examined with a critical mind. Rothwell’s initial analyses were post hoc interpretations of trial data, whereas the analyses presented in the current article in Stroke are interpretations of nonoutcome studies extrapolated to predict outcomes. Interpretative analyses are justified by the wish of understanding the mechanisms of a finding, in our case, the benefits of antihypertensive treatment. The obvious question, meritoriously raised by Rothwell himself, is what mechanisms are defined by the word “variability”? May the same word happen to be used with different meanings in different contexts?

In its common acception, blood pressure variability is intended as the frequent behavior-related changes in blood pressure from moment to moment or from 1 measurement to the next one, or from 1 hour to another, a phenomenon already described by Riva Rocci in his classical paper. This “short-term” variability was investigated in depth, particularly by our group in Milan, when ambulatory blood pressure measurement became possible. The Milan group also found the standard deviation of 24-hour measurements was correlated with organ damage in hypertension. In their analysis of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial, Rothwell and associates have confirmed that this “short-term” variability has predictive value for incident stroke, but to a much lesser extent than the 2 new variability indices.

Undoubtedly, in addition to the well-studied “short-term” variability, there also is a “longer-term” variability consisting of blood pressure changes from day to day, from season to season, or, in treated hypertensives, in blood pressure changes due to drug properties, individual responsiveness to drugs, treatment compliance, and variable success of therapy. This “long-term” variability is more difficult to measure, and for this reason, although its potential role has always been recognized, only lip service has been paid to it. Is this “long-term” variability that is now being measured by Rothwell’s intraidividual and/or interidividual variabilities?

At first glance, intraindividual visit-to-visit variability appears as a good candidate to measure this long-term blood pressure variability. However, when applied to outcome trials to investigate its outcome predictive ability, this index is calculated from measurements at wide time intervals (6 months in ASCOT) and whether it is measuring naturally occurring or treatment-induced blood pressure variability or persistency in treatment or compliance to treatment is difficult to decide. Paradoxically, supporters of the predictive role of mean achieved blood pressure can more easily dispense themselves from frequent measurements, whereas the same is not the case for investigators exploring the role of long-term variability. The ideal approach may rely on home blood pressure measurements that can be made daily or several times per week. In the meantime, the important observations made by Rothwell and his associates cannot be disregarded, but efforts should be made to better understand their physiological meaning, the phenomenon and the mechanism they do measure. The stroke-predictive role Rothwell et al have shown also for the maximum blood pressure value measured at any of the follow-up visits during an intervention trial cannot be taken as demonstration of the obnoxious value of occasional, often emotion-driven, surges in blood pressure with the consequence of crowding the already heavily crowded emergency rooms of our hospitals.

Separate consideration should be given to the other variability index calculated by Rothwell’s group and used in the article published in this issue of Stroke. Individuial variability has also been found to correlate with incident stroke in large outcome trials, and the authors have suggested to use it as a surrogate of intraindividual variability when individual data are not available. The SD or the variance of blood pressure values in a group of patients at a follow-up visit is another matter than individual variability on a large timespan. Group variance of blood pressure during treatment is likely to express variability in the blood pressure response to treatment of the various members of the group. I have previously suggested that even when the same average blood pressures are achieved in the 2 treatment arms of a trial, the distribution curves can be different, wider, or narrower and particularly more or less skewed to the right (nonresponders can hardly be matched in number by excessive responders). Width and skewness of the distribution curve will have an impact on outcome incidence, because it is known that blood pressure is related to outcomes in a nonlinear way (namely, semilogarithmically). The authors argue that inter- and intraindividual variability indices are strongly correlated (the latter would account for approximately 50% or perhaps more of the former) and therefore interindividial variability can safely be used as a surrogate of the intraindividual one. This does not deny that a surrogate is a surrogate and that the 2 measures, even if correlated, may have quite different meanings.

The use of interindividial as a surrogate of intraindividual variability may have further limitations when applied, like in the current article in Stroke, to small, short-lasting, nonoutcome pharmacological studies. The authors legitimately argue that for a specific class of antihypertensive agent, the group SD is similar in short-term studies and long-term trials. However, do similarities of indices calculated in such different contexts as individual visit-to-visit measurements during several years, group blood pressure distributions at visits during long-term follow-ups, or group blood pressure distributions only a few days or weeks after initiation of treatment allow the conclusion that what these various indices measure is really the same thing, the same mechanism, or the same variation? Can a practicing physician be easily persuaded that a blood pressure variability index measured only a few days or weeks from initiation of therapy really predict blood pressure variability during the large number of years chronic antihypertensive therapy must be continued? Can we safely exclude that similarities between different variability indices simply indicate they have some measurement in common (perhaps, average blood pressure?) that is too easily dismissed by excessive faith in statistical adjustments?
The conclusion of the current article that short-term, group blood pressure variability can identify the most effective drug or drug combination for individual prevention of stroke appears hazardous. This conclusion derives from calculating a surrogate (short-term group variability) of a surrogate (long-term group variability) of an index (long-term intrindividual variability), the meaning of which is still largely unknown (real variability, consistency of treatment effectiveness, treatment compliance?) and extrapolates these calculations from surrogates to outcomes such as stroke that did not occur nor could have occurred during the study period. This may be another case of wars substituted for by war games with dead bodies no longer counted on the battlefield but on a video screen. Although the statistical evidence provided by Rothwell and associates is imposing, and perhaps intimidating for a layman (such as I), a Clausewitz of hypertension may be tempted to doubt whether the war against hypertension is a too serious thing to be left to statisticians.

Joking aside, Rothwell and his associates deserve recognition for having raised an issue of the upmost conceptual and practical importance. The issue deserves to be studied in depth without hurrying to premature conclusions. More reliable indices of “real” blood pressure variability from day to day through the many years of treatment must be elaborated and investigated (perhaps by home blood pressure monitoring), and a better understanding of the phenomena underlying the current variable definitions of variability should be achieved.

Disclosures

None.

References


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