Rethinking guidelines for treating high blood pressure: Variability is a risk factor too

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Hypertension is the most prevalent treatable risk factor for stroke. One in two adults are affected by it, and the risk of being hypertensive during a lifetime is about 90%. Despite this, the underlying mechanisms by which raised blood pressure can cause cardiovascular disease are poorly understood. Clinical guidelines for the diagnosis and treatment of hypertension focus heavily on mean systolic blood pressure.

However, in this collection of papers in The *Lancet* (two Articles and a Review) and The *Lancet Neurology* (an Article), Peter Rothwell, at the Stroke Prevention Research Unit, John Radcliffe Hospital, Oxford, UK, and colleagues suggest that variability in blood pressure could also have some prognostic value. "The hypothesis that has come to dominate is that we each have an underlying average "true" blood pressure, which is difficult to measure precisely, but which accounts for the vast majority of the complications of hypertension, and explains the benefits of blood-pressure-lowering drugs. Variability in blood pressure is dismissed as uninformative and "random", only noteworthy as an obstacle in the measurement of the true underlying blood pressure," says Rothwell.

In one Article, a cohort study, Rothwell's team found that visit-to-visit variability of systolic blood pressure was a strong predictor of stroke, heart failure, angina, and myocardial infarction, independent of mean blood pressure. By contrast with assumptions in current guidelines that patients with only occasional high readings ("episodic hypertension") do not require treatment, they show that such patients have a high risk of stroke and other complications. In this study, they investigated variability

in blood pressure and maximum blood pressure in four cohorts with previous transient ischaemic attack (each cohort had more than 2000 patients). In one cohort, the researchers also looked at whether residual variability after treatment for hypertension would be a predictor of stroke.

They found that patients with the most variation in systolic blood pressure over seven clinic visits were six times more likely to have a stroke. Patients with the highest blood pressure over seven visits were 15 times more likely to have a stroke. Rothwell says that: "Persistent hypertension is a major cause of vascular disease and must be treated appropriately, but episodic hypertension is at least as common in routine practice and should no longer be ignored. We have shown that episodic hypertension is just as risky, and that patients and their doctors shouldn't be reassured by the fact that blood pressure is sometimes normal."

In a separate Article, a meta-analysis of 389 randomised controlled trials comparing the effects of blood-pressure-lowering drugs, Rothwell and other colleagues showed that drug-class effects on variability in blood pressure explain differences between these drugs in their efficacy in preventing stroke, and they introduce the idea of blood-pressure stabilising drugs. "Compared with other drug classes, calcium-channel blockers and non-loop diuretic drugs reduced interindividual variation in systolic blood pressure, whereas ACE inhibitors, angiotensin-2-receptor blockers, and β blockers increased it, with calcium-channel blockers reducing interindividual variation the most versus placebo," say the authors.

In an Article in The Lancet Neurology, Rothwell and colleagues investigate why calcium-channel blockers reduce the risk of stroke more than expected on the basis of mean blood pressure alone, and why β blockers are less efficacious than expected. The researchers analysed the results of two large trials (one comparing amlodipine with atenolol in 19

257 patients with hypertension and other vascular risk factors, and one comparing atenolol and diuretics versus placebo in 4396 hypertensive patients aged 65 years). The authors say "The opposite effects of calcium-channel blockers and β blockers on variability of blood pressure account for the disparity in observed effects on risk of stroke and expected effects based on mean blood pressure."

In a Review, Rothwell "discusses shortcomings of the usual blood-pressure hypothesis, provides background to accompanying reports on the importance of blood-pressure variability in prediction of risk of vascular events and in accounting for benefits of antihypertensive drugs, and draws attention to clinical implications and directions for future research."

In a Comment in The *Lancet* on all the papers, Dr Bo Carlberg and Dr Lars Hjalmar Lindholm, Department of Public Health and Clinical Medicine, Umeľ University Hospital, Sweden say: "Importantly, Rothwell and co-workers do not question the importance of mean blood pressure; rather, they make a strong argument for also measuring blood-pressure variability because it supplements blood pressure very well as a risk factor."

They add: "further study of the relation of blood-pressure variability to the risk of different types of stroke (eg, cardioembolic, large-vessel disease, and small-vessel disease, etc) is important."

Carlberg and Lindholm conclude: "Should indications for starting or escalating treatment of hypertension be updated, taking into account episodic high blood pressure? Not quite yet, because results from clinical trials with standardised recordings and treatment care are difficult to translate into every day practice in which patients often receive several different drugs, often changing over a short time. The notion presented by Rothwell and co-workers today is, however, challenging and will raise

many questions. Researchers with data from population-based cohorts or randomised trials are likely to investigate whether Rothwell's findings can be replicated, taking other risk factors into account."

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