White-Coat Hypertension and Risk of Stroke
Do the Data Really Tell Us What We Need to Know?

Paul W. Franks

The term “white-coat hypertension” (WCH; also commonly referred to as isolated office hypertension) describes the transient increase in blood pressure (BP), resulting from an alerting reaction and pressor response, observed in certain individuals when attending a clinic or doctors’ office.1 The diagnosis of WCH is usually ascribed when clinic BPs exceed 135/85 mm Hg and average daytime BPs do not. WCH could be dismissed as a risk factor for stroke and other cardiovascular events, because the increase in BP is transient and may be idiosyncratic to the clinic setting.2 However, WCH may be a marker of stress reactivity per se, because surges in BP that occur in the doctor’s office are indicative of BP surges in other stressful scenarios.3

The article by Verdecchia et al featured in this edition of Hypertension4 reports data from 6000 Italian, Japanese, and American adults. The purpose of the study was to explore the relationship between classically defined WCH and incident stroke during a median follow-up of 5.4 years. When compared with normotensive controls, a tendency for increased stroke incidence was observed in patients with WCH (unadjusted hazard ratio, 1.15). However, because the variance around the estimates of effect is large (95% confidence interval, 0.61 to 2.16), this association is not statistically significant, despite this study being the largest of its kind to date. By contrast, a statistically significantly association between ambulatory hypertension and stroke was observed (unadjusted hazard ratio, 2.01; 95% confidence interval, 1.31 to 3.08).

The hypothesis that Verdecchia et al test is important because vessels in the brain may be particularly susceptible to transient elevations in BP. Furthermore, because WCH is highly prevalent,5 even a relatively small increase in stroke risk on an individual level could convey a high population-attributable risk. Although Verdecchia et al have demonstrated using conventional methods that WCH does not significantly increase the risk of stroke, as they point out, this observation may not preclude a causal role for WCH in stroke risk. This is because, despite the impressive size of the study, it may be statistically underpowered to test the hypothesis, as indicated by the wide confidence limits around the error estimates.

The principle factors that determine statistical power in the study of WCH and stroke, aside from sample size, are (1) the magnitude of the effect (ie, the extent to which WCH increases the risk of stroke); (2) the precision with which the exposure (ie, WCH) and the outcome (ie, stroke) are measured; and (3) the manner in which these data are analyzed statistically.

Of the classical risk factors for cardiovascular disease, BP is one of the more easily measured. The procedure is relatively easy to perform, is of low invasiveness, and its quantification is immediate. However, the extent of agreement between serial measures of BP within-individual (ie, the intraclass correlation) is among the lowest of the classical risk factors.6 This high variability affects the probability of detecting a true effect of BP on disease. Thus, identifying the factors that cause BP to appear so variable is important.

As demonstrated by Mayo,7 when people are aware that they are being observed, their behavior alters. Thus, although the effects of measurement error and bias can be minimized through careful experimental design and statistical adjustment, these effects cannot be completely attenuated. Hence, to determine whether an association between WCH and stroke is real, one must first consider whether error and bias could explain the observation.

In the case of clinical traits such as BP, the magnitude of the measurement error will depend partly on the accuracy of the equipment and/or the skill of the observer. However, at least in terms of ambulatory BP monitoring, the interinstrument variability in the estimates obtained is not large.8 Thus, factors other than equipment or observer error, which are inherently characteristic of BP, are largely responsible for its low intraclass correlation; one such factor is biological flux (ie, the marked moment-to-moment variation in BP caused by changes in factors such as the volume and force of cardiac contraction, compliance of large blood vessels, and total systemic vascular resistance). This high degree of biological variability influences both the extent to which BP measured at a given time represents usual BP, which is an important exposure in terms of cardiovascular risk per se, and the probability of recording peak BP, which may be an important exposure in stroke risk.9

The difference between the average 24-hour BP and the BP measured at any point during that period may vary by as much as ±30%, whereas in the same context, variation in other traits such as weight is several-fold lower. However, using the mean of repeat measurements of...
BP will decrease this variability. The more measures made, the closer the mean of the measures will be to the true usual BP, and the greater the probability that one of these measurements will closely approximate the peak BP. Thus, independent of stress reactivity, BP measured in the clinic (assuming it is not continuously measured) will differ from the usual BP to a greater extent than the mean ambulatory BP. This has several implications for interpreting the relevance of WCH in relation to stroke risk.

In population studies in which the diagnostic procedures are uniform, the high degree of error that accompanies clinic-measured BP will serve to decrease the probability of detecting a true association. On an individual basis, the probability of diagnosis will be inversely proportional to the number of times the diagnostic procedure is undertaken. The probability of observing WCH on consecutive occasions, which is often used as a standard by which clinical diagnoses are made, will be low. Thus, in practice, false-negative diagnoses of WCH using conventional approaches likely occur frequently. The consequence of this phenomenon on both an individual and population basis will be to underestimate the magnitude of the risk conferred by WCH on disease and early mortality.

Although statistical power will be improved in studies of WCH that continuously measure BP during the clinic visit, elevations in clinic BP (and BP measured elsewhere) are partly attributable to the Hawthorne effect (ie, a change in voluntary or involuntary behavior resulting from the knowledge that one is being observed). Typically, the more invasive the subject perceives the observation to be, the greater the change in behavior and consequent stress response. For example, clinic BP is generally higher when assessed by a physician than by a nurse, presumably because the patient perceives the measurement taken by the nurse to be less invasive. Therefore, although the continuous assessment of clinic BP may improve statistical power, it could, if perceived by the patient to be especially invasive, result in a hypertensive episode, as has been shown with ambulatory monitoring outside the clinic setting.

This would clearly influence the probability of diagnosing WCH, but it is an effect that would be inconsistent across individuals and hence difficult to quantify.

Because the relationship between BP and stroke is graded and continuous, from a pathophysiological perspective, the standard categorical definition of hypertension is without a biological basis. This is also true of the standard definition of WCH. Although in clinical practice categories are useful, treating BP as a categorical trait rather than a continuous trait in statistical analyses will lower the power to detect an effect. Thus, prevention of adverse events from WCH could include strategies designed to prevent these potentially effect-modifying behaviors. However, if elevated BP is purely a passenger with other forms of stress reactivity, such as catecholamine-invoked lipolysis or decreased heart rate variability, both of which are themselves risk factors for cardiovascular disease, then without concurrent measurement of these factors and adjustment in analyses it is impossible to know whether WCH is truly causally related to disease.

In summary, overcoming the problems of measurement error, response bias, and confounding that hinder studies seeking to test the association between WCH and the risk of stroke and other cardiovascular diseases will likely require more than just bigger studies. The methods of measuring BP will probably need to improve, as will the statistical approaches used to test association. When possible, BP monitoring devices, whether for use in the clinic or elsewhere, should be unobtrusive to the patient and record BP continuously, and data derived from these devices should be analyzed on a continuum. Further thought should also be given to the assessment and characterization of the outcome, stroke, because this will also affect the detection of an effect. Thus, even with the dearth of supportive epidemiological evidence, it is probably inappropriate at this time given the issues described to discount the possibility that WCH increases the risk of stroke and its comorbidities.

References

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