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COMMENTARY

From casual blood pressure measurement to long-term blood pressure burden: better elucidation of the association between versatile blood pressures and cardiovascular events

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High blood pressure is the most important controllable risk factor for various cardiovascular diseases, especially stroke. It is of particularly importance for the Asian populations given their well-known propensity for the development of stroke.[1] Despite a plethora of evidence showing that high blood pressure is closely related to the risk of cardiovascular disease, it is very intriguing that we are still not certain which location of blood pressure (radial, brachial or central), which component of blood pressure (systolic, diastolic or pulse) and which time period of blood pressure (daytime, nighttime or clinic) are most predictive and, therefore, clinically relevant. In this issue of the journal, Sasai *et al.*[2] assessed the predictability of another important, and equally intriguing, aspect of high blood pressure, the long-term blood pressure burden, for cardiovascular and all-cause mortality in 46 484 Japanese people free of prior cardiovascular diseases followed up for 7 years. They used averaged two blood pressure measurements taken 5 years apart as a proxy for long-term blood pressure burden. Overall, they found that this index of long-term blood pressure burden was associated with a greater risk of cardiovascular mortality than either casual blood pressure measurement alone.

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Blood pressure itself is a highly variable parameter. Individuals are exposed to varying blood pressure levels during their lifetime. It is hence hard to conceive that a single casual measurement of such a highly variable parameter is sufficient to investigate the relations of blood pressure and the risk of cardiovascular diseases. To better profile the long-term burden of the versatile blood pressure, there are mainly three different statistical approaches developed (Figure 1). We will then briefly describe these three approaches and discuss the value of the study done by Sasai *et al.*[2] under this context.

First, it is traditionally assumed that every individual should have an underlying 'usual' blood pressure, which primarily accounts for all blood pressure-related vascular risk and for the benefits of antihypertensive drugs (the usual blood pressure hypothesis).[3–4] Fluctuations in blood pressure are regarded as noise and merely an obstacle to reliable estimation of usual blood pressure. It is postulated that such fluctuations in the characterization of blood pressure can result in substantial underestimation of the strength of the real association between usual blood pressure and cardiovascular risks, the so-called 'regression dilution' bias.[3–4] Information from repeat measurements of blood pressure in Western population studies, like the Framingham and the Puerto Rico studies, showed that the difference in mean blood pressure between the top and bottom categories is about 60% greater for baseline blood pressure than for blood pressure remeasured 4 or more years later (the phenomenon of 'regression to the mean').[3] Hence, the slopes of the real associations between usual blood pressure and cardiovascular risks might be at least 60% steeper than when the relative risks or hazard ratios are plotted against baseline blood pressure (the 'regression dilution' effect).[3] However, it has to be emphasized that this direct translation of the 'regression to the mean' effect on casual blood pressure measurement into the 'regression dilution' effect on cardiovascular risk prediction needs to be validated by analyzing the associations between 'true' usual blood pressure and the risk of cardiovascular diseases.[5]

In addition, it is still not certain whether the scale of the 'regression to the mean' effect on casual blood pressure measurement is similar between Western and Asian populations because the scale is determined by the extent of fluctuations of blood pressure in a given population. Accordingly, it would be of more importance to elucidate whether casual blood pressure measurement underestimates the strength of associations between usual blood pressure and cardiovascular diseases to the same extent in different populations. In the study done by Sasai *et al.*, even though they did not analyze their data to examine the magnitude of the 'regression to the mean' and 'regression dilution' effects, we can still glimpse it by viewing the averaged two blood pressures taken 5 years apart as a proxy of 'usual' blood pressure. Surprisingly, the hazard ratio (for cardiovascular mortality) associated with averaged blood pressure is approximately 60% greater than that associated with baseline blood pressure in this Japanese population-based study, irrespective of the use of antihypertensive drugs.[2] The

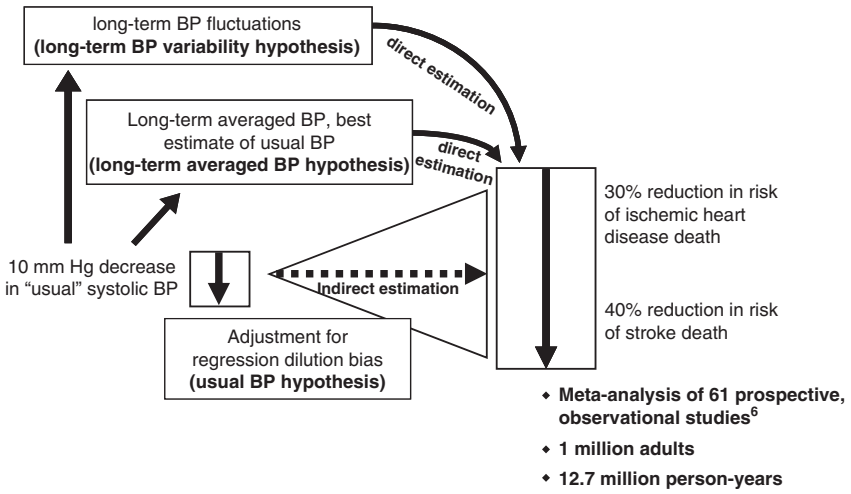

Figure 1 Three different statistical approaches to profile the long-term burden of the versatile blood pressure. In the 'usual blood pressure hypothesis' model, the risk relations associated with usual blood pressure are indirectly calculated by adjusting the risk relations associated with baseline casual blood pressure for regression dilution ratios obtained from repeat measurements of blood pressure during prolonged follow-up,[3,6] rather than directly using actual mean blood pressure of each individual.

implications of this finding are (1) the 'regression dilution' effect of casual blood pressure on cardiovascular mortality does exist in the Japanese population, (2) the magnitude of the regression dilution effect ($\sim$60%) observed in the Japanese population is similar to that reported in Western populations[3,6] and (3) the magnitude of the 'regression to the mean' effect on blood pressure measurement might be similar between Japanese and Western populations although it was not assessed directly as the 'regression dilution' effect in this study. Taken together, the more pronounced predictability of averaged blood pressure shown in the Sasai's study further substantiates the prognostic significance of usual blood pressure in Asian populations.

Second, atherosclerotic cardiovascular diseases evolve slowly and are related to cumulative exposure to various risk factors over a lifetime. Therefore, investigators have used long-term ($>$1 year to decades) time-averaged blood pressure for characterizing cumulative blood pressure exposure and assumed that time-averaged blood pressure would be the main determinant of blood pressure-related adverse events (long-term averaged blood pressure hypothesis).[7] Several studies have demonstrated that time-averaged blood pressure is a better predictor of echocardiographic left ventricular hypertrophy,[8] the degree of carotid stenosis[9] and the incidence of various cardiovascular diseases above and beyond current casual blood pressure,[7] thus proving its prognostic value. In fact, time-averaged blood pressure not only reflects long-term blood pressure burden, it actually provides the best estimate of usual blood pressure in a given individual.[5] In this respect, the long-term averaged blood pressure hypothesis and the above-mentioned usual blood pressure hypothesis are essentially the same. More specifically, the long-term averaged blood pressure hypothesis could be viewed as the *bona fide* usual blood pressure hypothesis, given that time-averaged blood pressure (or actual mean blood pressure) is indeed the most accurate estimate of usual blood pressure.

In the study done by Sasai *et al.*,[2] the time-averaged blood pressure is composed of only two measurements taken 5 years apart. Modeling studies show that at least 7–10 measurements of blood pressure at different time points are needed for mean blood pressure to be an accurate estimate of usual blood pressure and long-term blood pressure burden.[5] The inadequate sampling number of blood pressure measurements may limit the predictability of time-averaged blood pressure. This may, in part, explain why the hazard ratios with time-averaged blood pressure for cardiovascular mortality in this study are only about one-half of those reported in the Framingham study and the meta-analysis of individual data for one million adults in 61 prospective studies (Figure 1).[6,7] To demonstrate the incremental prognostic value of long-term averaged blood pressure over current casual blood pressure, current blood pressure should be adjusted in the statistical model.[7] Because there are only two blood pressure measurements available in this study, this adjustment is obviously not possible to provide any useful information. Moreover, it is still debatable regarding whether there is a threshold level of blood pressure for cardiovascular risks.[6] It would be of interest to explore this threshold issue in time-averaged blood pressure, which apparently better characterizes the long-term blood pressure burden.

Third, in addition to usual blood pressure and long-term time-averaged blood pressure, which are relatively static components of blood pressure, recent studies have shown that long-term blood pressure variability adds important prognostic information (long-term blood pressure variability hypothesis),[5,10] which corresponds nicely with the versatile nature of blood pressure. It is well known that short-term variability of blood pressure, with use of 24-h ambulatory monitoring or home blood pressure recordings, predicts cardiovascular risk.[11] Furthermore, long-term blood pressure variability, as represented by s.d. of long-term clinic blood pressure measurements or maximum blood pressure reached, has been shown to independently and even more strongly associated with cardiovascular risk compared with long-term averaged blood pressure.[5,10,12] Other evidences supporting the blood pressure variability hypothesis include that patients with only episodic hypertension are at a high cardiovascular risk, that residual visit-to-visit variability in blood pressure on treatment has poor prognosis despite good control of mean blood pressure, and that benefits of some antihypertensive drugs are due partly to reduced variability in blood pressure.[10]

The assumption that variability (fluctuations in blood pressure) is of prognostic value contradicts the concept of usual blood pressure hypothesis, in which variability is deemed random.[3,4] However, the blood pressure variability hypothesis actually complements the usual blood pressure hypothesis: the discrepancy between risk relation adjusted for regression dilution bias and that with actual mean blood pressure might be attributable to the prognostic value of blood pressure variability.[5] Likewise, the less predictive hazard ratios with time-averaged blood pressure in the study done by Sasai *et al.* might be due partly to the lack of contribution from long-term blood pressure variability.

We congratulate Sasai *et al.*[2] for providing us the long-waited piece of the puzzle that time-averaged blood pressure has an important role in predicting cardiovascular mortality above casual blood pressure measurements in the Asian population. On the other hand, we have to point out that sizable residents excluded at first and second surveys, limited age inclusion criteria (40–79 years

only) and exclusion of subjects with certain preexisting cardiovascular diseases (a history of heart disease, stroke or atrial fibrillation) had diminished the generalizability of their findings. Despite use of antihypertensive drugs between two surveys were recorded and analyzed, it could partly reflect the long-term exposure of antihypertensive drugs between the survey periods. Finally, the accuracy of causes of death relying on death certificate remained debatable.[13]

In summary, given the highly versatile nature of blood pressure and its long-term impact, it is time to shift our focus from casual blood pressure to better profiling the long-term blood pressure burden. Recent evidence suggests that long-term average of blood pressure as well as long-term variability of blood pressure both provide complementary prognostic implications in different populations. Future researches regarding the causes, consequences and treatment of both long-term blood pressure parameters should be advocated to optimize our understanding and management of the inherently unpredictable hypertension.

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