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COMMENTARY

Questionable link between normo- to microalbuminuria and home-measured blood pressure variability in hypertension

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The accumulated results of clinical trials have shown that the strict control of blood pressure (BP) is essential for preventing target organ damage and reducing cardiovascular mortality in hypertensive patients (Figure 1). Although hypertension is usually diagnosed based on measurements of BP recorded during a visit to a physician (that is, office BP), several studies have shown that target organ damage and prognosis are more closely associated with ambulatory BP or home BP than with office BP. At present, hypertensive patients with albuminuria are increasing in number and cardiovascular complications are the most common cause of death in these hypertensive patients with albuminuria. Thus, it would be of considerable value to identify the mechanisms involved in the cardiovascular events associated with hypertension complicated with albuminuria.

Ambulatory BP monitoring has allowed an easier and more accurate determination of the circadian rhythm of BP in various pathophysiological conditions. The circadian pattern of BP in hypertensive patients with overt albuminuria has been found to exhibit a blunted nocturnal decrease in BP. The loss of nocturnal BP dipping has been considered to be a risk factor for the progression of nephropathy and of prognostic value with respect to target organ damage and cardiovascular morbidity.[1–3]

Ambulatory BP monitoring allows the acquisition of valuable information not only about the average BP over 24 h (the 24-h BP) but also about the variations in the BP values during the course of the day. Using information from ambulatory BP monitoring, previous studies have found that BP variability is a complex phenomenon that involves both short- and long-lasting changes.[4] Over 24 h, BP varies not only because of the decrease during nighttime sleep and the increase in the morning but also because of sudden, fast, short-term changes that occur during the day and, to a lesser extent, at night. This phenomenon, called short-term BP variability, has been shown to depend on sympathetic vascular modulation and atherosclerotic vascular changes. Several previous animal studies have shown that exaggerated short-term BP variability without significant changes in mean BP induces chronic cardiovascular inflammation and remodeling.[5,6] Short-term BP variability has also been suggested to be clinically relevant because hypertensive patients with similar mean 24 h BP values exhibit more severe organ damage when their short-term BP variability is greater.[7–14]

With respect to home-measured BP, several clinical studies (both long-term follow-up surveys and cross-sectional studies) have provided an epidemiological basis for supporting the greater accuracy of home BP monitoring than clinic BP measurement for the prognosis of fatal and nonfatal cardiovascular disease (CVD). There is a general consensus that home BP monitoring is more convenient, more readily available and less costly than ambulatory BP monitoring, but ambulatory BP monitoring has been recognized to be superior for certain clinical problems, for example, for the detection of non-dippers or sleep BP in patients with chronic renal disease, autonomic neuropathies or sleep apnea, and for the estimation of short-term BP variability.[15]

Concerning the variability in home BP, a study of the general population of Ohasama showed that high day-by-day BP variability is associated with increases in total, cardiovascular and stroke mortality, independently of the average BP value and other cardiovascular risk factors.[16] A recent study of 1866 Finnish adults also demonstrated that greater variability in morning home BP is an independent predictor of cardiovascular events.[17] With respect to a possible relationship between home BP variability and renal deterioration in hypertensive patients, a previous study demonstrated that home BP variability correlated with macroalbuminuria (urinary albumin excretion (UAE) $\geqslant$ 300 mg g^{-1} creatinine) independently of the known risk factors for type 2 diabetic nephropathy.[18] Thus, day-by-day home-measured BP variability is a candidate as an important factor in hypertension with diabetic nephropathy in a rage of macroalbuminuria.[19]

By contrast, a recent study reported that day-by-day BP variability, as assessed by home BP measurements, had no significant association with the progression of chronic kidney disease.[20] In line with this finding, the current study by Hoshide *et al.*[21] of Kario's Laboratory, which was performed as a post-hoc sub-analysis of the Japan Morning Surge-Target Organ Protection (J-TOP) study, failed to find a significant association

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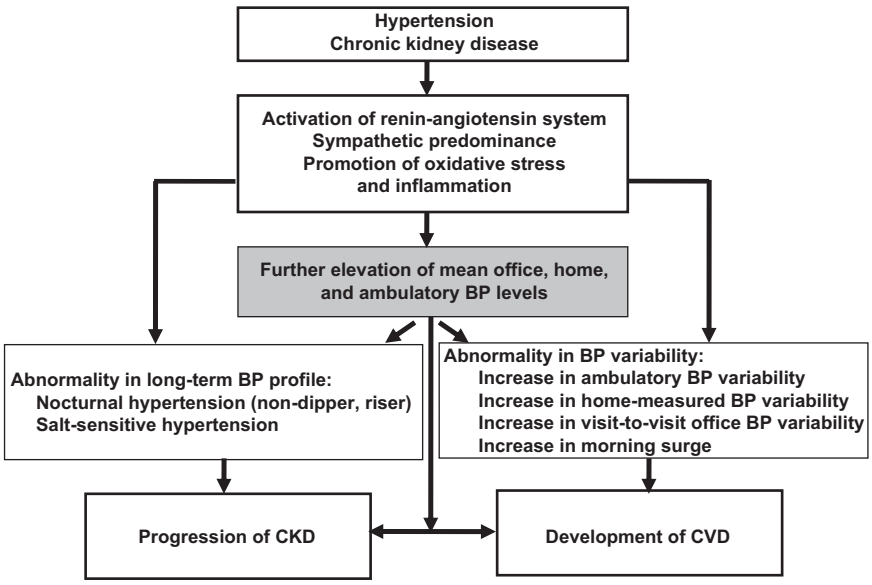

Figure 1 Schema showing the proposed importance of mean BP levels, long-term BP profile and BP variability in office BP, home BP and ambulatory BP measurements on the pathophysiological link between hypertension and chronic kidney disease.

between the improvement in home BP variability and the reduction of normo- and microalbuminuria (baseline UAE mg g^{-1} creatine (interquartile range), 18.9 (9.1–48.5)), in spite of a significant association between home BP variability and UAE at baseline, and questioned the clinical relevance of home BP variability in the progression of albuminuria, in a range of normo- to microalbuminuria in hypertensive patients. The findings by Hoshide *et al.* would be also consistent with a previous report from the same Kario's Laboratory showing a relatively weak association between home BP variability and albuminuria in a range of normo- to microalbuminuria, which is in contrast to the strong association that has been observed between home BP variability and cardiac hypertrophy in a cross-sectional study.[22] It is likely that the kidneys might not be affected by a transient increase in BP, as long as auto-regulatory mechanisms are functioning normally.

In addition, in clinical trials, such as the RENAAL and IDNT trials, a reduction in overtly increased albuminuria significantly improved CVD outcomes in macroalbuminuric subjects (UAE $\geqslant$ 300 mg g^{-1} creatinine).[23] However, several clinical studies, including the ONTARGET, TRANSCEND and ACCOMPLISH trials, revealed that reductions in microalbuminuria do not necessarily translate into a reduction in CVD in patients with normo- and microalbuminuria, particularly when accompanied by a significant long-term decrease in estimated glomerular filtration ratio (eGFR; usually more than 30% decrease in eGFR during 3 months after the start of intervention). Therefore, UAE in the range of normo- to microalbuminuria (UAE $<$ 300 mg g^{-1} creatinine), as found in the study by Hoshide *et al.*, may not reflect target organ damage and may not be acceptable as a surrogate marker for nephropathy progression and/or CVD development in hypertensive patients, particularly in non-diabetic patients.[24]

Furthermore, recently published systematic reviews have shown that ambulatory BP monitoring is superior to home BP monitoring and clinic BP measurements in terms of diagnostic accuracy and cost effectiveness, even in a primary care setting.[25,26] The hypothesis that home BP variability favors the development of renal deterioration in hypertension is appealing. However, further studies are warranted to explore the prognostic potential of home BP variability. These studies could include outcome studies focusing on whether a therapeutic intervention that reduces home BP variability carries an additional prognostic benefit to lowering the average home BP levels, as well as close comparisons of home BP variability and ambulatory BP variability in terms of diagnostic and prognostic accuracy and cost effectiveness.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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