Hypertension Research (2013) 36, 112–114
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www.nature.com/hr

COMMENTARY

Slowing chronic kidney disease progression: should we be looking beyond mean blood pressure?

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Hypertension Research (2013) **36,** 112–114; doi:10.1038/hr.2012.167; published online 11 October 2012

Chronic kidney disease (CKD) is increasingly being recognized as a major global public health concern. This is perhaps best evidenced by the establishment of World Kidney Day, which has been observed annually since its inauguration in March of 2006. Preceding this global CKD awareness campaign, the introduction of the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation in February of 2002 propagated an important global shift towards the recognition of CKD as a worldwide public health problem that should be screened and managed by clinicians.[1] Although we have a better understanding of the alarming incidence and prevalence of CKD in various world populations as a result of these efforts, effective treatment strategies to slow or even halt the progression of CKD are still limited. Presently, once significant impairment of renal function has occurred, the progression of CKD toward end-stage renal disease (ESRD) tends to occur irrespective of pharmacologic treatment in many individuals. Thus, although current treatment guidelines have undeniably been beneficial in reducing the incidence of ESRD, there is much still to be discerned regarding the effective treatment of CKD.

Hypertension is one of the leading factors that contributes to the progressive decline of renal function leading to ESRD, and thus has become an important target in the treatment of CKD. Current guidelines recommend a target clinic blood pressure (BP) of $<130/80$ mm Hg for patients with CKD.[2] These guidelines stem from findings from observational studies and clinical trials that suggest that lowering mean BP may slow or retard the progression of CKD and reduce concurrent cardiovascular risk.[3–6] However, several large-scale randomized controlled trials have reported that there is no significant beneficial effect of intensive BP lowering of $<130/80$ mm Hg for patients with CKD.[7,8] From these latter findings, it has been suggested that once mean BP is lowered to a given level, additional reductions do not confer greater protection against CKD progression.[8] Although the lowering of BP is still regarded as one of the main goals for CKD treatment despite these findings, nonetheless they raise questions as to what is the most effective pharmacologic approach for treating BP in CKD patients.

In recent years, data have accumulated to indicate that changes or fluctuations in BP values across weekly, monthly or yearly clinic visits may have prognostic value that is equal to or greater than that of mean BP. In a retrospective analysis of 22 576 patients with essential hypertension enrolled in the International Verapamil–Trandolapril Study trial, it was found that for a given mean BP level, there was an inverse relationship between the risk of cardiovascular morbidity and mortality, and the percentage of clinic visits in which BP was found to be controlled (that is, $<140/90$ mm Hg). From these findings, it was concluded that focusing not only on mean BP, but also on the proportion of visits in which BP was controlled may improve the assessment of the protective effect of BP-lowering interventions on patient outcome.[9] In a more comprehensive analysis in which the visit-to-visit changes in BP were quantified as an index of variability (e.g., visit-to-visit BP variability), retrospective analysis of both the UK-TIA aspirin trial and Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) by Rothwell *et al.*[10] showed that visit-to-visit variability in systolic BP over the course of five or seven clinic visits predicted stroke/coronary events to a much greater extent than mean BP. Furthermore, in two separate retrospective analyses of randomized controlled trials, it was shown that the treatment regimens associated with lower visit-to-visit variability in systolic BP were also associated with a lower incidence of stroke and accounted for more of the effects of treatment efficacy on stroke risk than did effects on mean BP.[11,12] These findings have led some to suggest that pharmacologic therapy targeting BP should reduce mean BP without increasing BP variability, and ideally should reduce both.[11] In light of these findings, the question as to whether visit-to-visit BP variability should be a target in CKD management may be worth exploring as it could help to explain previous study findings that reported a lack of additional benefits with aggressive BP lowering and could help to provide direction as to the optimal pharmacologic regimens for CKD treatment.

In this issue of *Hypertension Research*, Yokota *et al.*[13] investigate for the first time the longitudinal effect of visit-to-visit BP variability on the progression of CKD. They report that the variability in BP across 12 consecutive visits taken over a median of 24 months was an independent predictor of the slope of decline in estimated glomerular filtrate rate (eGFR). They furthermore showed that the risk for composite renal end points (doubling of serum creatinine or need for dialysis) doubled for each 1 mm Hg increase in the visit-to-visit variability of systolic BP. Perhaps more surprisingly, they show that mean BP was not a predictor of the eGFR slope or composite renal end points after adjustment

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for covariates in this cohort of patients with non-diabetic CKD. Taken together, these findings may provide some evidence that visit-to-visit BP variability is associated with the progression of non-diabetic CKD. Of course, given the small size of the study cohort ($n = 56$), these findings will need to be confirmed in much larger clinical trials. Nonetheless, they do shed light on a potential therapeutic target in CKD that extends beyond the conventional management of mean BP.

Although the findings presented by Yokota *et al.* are interesting and certainly could suggest that clinicians should be paying attention to more than just mean BP when treating CKD, their findings perhaps raise more questions than answers. First, what are the mechanisms by which large fluctuations in BP contribute to the progressive deterioration of renal function? Data from several cross-sectional studies have reported an association between visit-to-visit BP variability and alterations in the structure and function of the vasculature, which might suggest that increased variability in BP could contribute to the pathogenesis of vascular dysfunction in the renal microvascular.[14,15] Alternatively, it is plausible that visit-to-visit variability in BP could simply be the manifestation of inconsistent medication adherence. Unfortunately, measures of vascular structure/function and medication adherence were not assessed in the present study; thus the precise mechanisms remain to be elucidated. Second, when is a patient considered to have high visit-to-visit BP variability that mandates treatment? Yokota *et al.* attempted to address this issue in their study using the Youden Index to identify a clinical cut point for the visit-to-visit variability in systolic BP. They identified the cutoff value of 14.8 mm Hg as an indicator of the composite renal end points with a sensitivity and specificity of 86% and 63%, respectively. Nonetheless, the low sample size in their study and the moderate level of specificity for predicting composite renal end points limits this cut point's clinical relevance. Third, how frequently should BP be measured? Several studies on visit-to-visit BP variability have shown that the variability in BP quantified from annual visits is associated with clinical outcomes;[16,17] whereas others have reported visit-to-visit variability quantified from visits spanning a period of weeks to months is associated with clinical outcomes.[10,18,19] Unfortunately, this question could not be addressed adequately, given the retrospective nature of the study by Yokota *et al.*, as the duration between clinic visits was not static within-subjects or between-subjects. Nonetheless, one could infer from their findings that the frequency of visits is not a confounding factor as the association of visit-to-visit BP variability with measures of CKD progression remained significant after adjustment for the mean duration between visits in multivariate models. It is worth noting, however, that a previous study by Okada *et al.*[20] reported that the day-to-day variability in BP measured over 7 consecutive days with a home BP monitoring device was not associated with CKD progression in a cohort of 135 patients with stage 3–5 CKD. Whether the conflicting results from these two studies is a result of differences in study population or whether it might suggest that changes in BP over a period of months carries greater prognostic value in CKD than changes in BP over a period of days is still unclear. Finally, if both mean BP and BP variability should be targeted for pharmacologic treatment in CKD patients, what type of antihypertensive drug or drug combination would carry the greatest therapeutic effect? In the study by Yokota *et al.*, although the use of calcium channel blockers was associated with the steepest declines in eGFR, no differences were reported in visit-to-visit BP variability across drug classes. Thus, their findings provide little evidence or insight as to whether the effects of pharmacologic treatment on visit-to-visit BP variability confers any benefit. It should be acknowledged, however, that the study was grossly underpowered to appropriately investigate drug class effects.

In conclusion, whether we should consider visit-to-visit BP variability as an additional target for antihypertensive treatment in CKD patients, along with the reductions in mean BP, still remains unclear and the available evidence is not strong enough to support such a conclusion. Findings from experimental studies in animal models have reported that reductions in BP variability by various antihypertensive treatment regimens are associated with organ protection of the heart, kidneys and aorta, independent of effects on mean BP.[21–23] However, evidence that BP variability reduction from antihypertensive treatment improves prognosis in CKD in human subjects presently does not exist. The study by Yokota *et al.* provides important information about an emerging cardiovascular risk factor and presents some of the first evidence that visit-to-visit BP variability may have clinical or prognostic value in CKD. The many questions that their findings raise warrants further investigation, perhaps starting with re-analysis of large-scale observational studies and randomized controlled trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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