

Ambulatory Blood Pressure and Cardiovascular Events in Chronic Kidney Disease

Rajiv Agarwal, MD

Summary: Hypertension is an important risk factor for adverse cardiovascular and renal outcomes, particularly in patients with chronic kidney disease (CKD). This review compares blood pressure (BP) measurements obtained in the clinic with those obtained outside the clinic to predict cardiovascular and renal injury and outcomes. Data are accumulating that suggest that ambulatory BP monitoring is a superior prognostic marker compared with BP values obtained in the clinic. The use of ambulatory BP monitoring can detect white-coat hypertension and masked hypertension, which results in less misclassification of BPs. Ambulatory BP monitoring is a marker of cardiovascular end points in CKD. Nondipping is associated with proteinuria and lower glomerular filtration rate. Although nondipping is associated with more end-stage renal disease and cardiovascular events, adjustment for other risk factors removes the prognostic significance of nondipping. For patients with CKD who are not on dialysis, 24-hour ambulatory BPs of less than 125/75 mm Hg, daytime ambulatory BP of less than 130/85 mm Hg, and nighttime ambulatory BPs of less than 110/70 mm Hg appear to be reasonable goal BP targets. In the management of hypertension in patients with CKD, control of hypertension is important. Ambulatory BP monitoring may be useful to assign more aggressive treatment to patients with masked hypertension and withdraw antihypertensive therapy in patients with white-coat hypertension. Ambulatory BP monitoring can refine cardiovascular and renal risk assessment in all stages of CKD. The independent prognostic role of nondipping is unclear.

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Hypertension is a strong, modifiable, cardiovascular risk factor. Nearly all clinical decisions in hypertension are made using clinic blood pressure (BP) recordings because the vast majority of cardiovascular risk assessment and antihypertensive trials were performed using these measurements. However, BP measurements can be obtained in the clinic, by self-measurement at home, and by automated ambulatory BP recordings.¹ These recording methods have led to the recognition

of hypertension that depends on the environment in which the BP measurements are made. White-coat hypertension and masked hypertension are 2 types of situational hypertension. White-coat hypertension is defined as high BP values in the clinic and normal BP values by ambulatory BP monitoring, whereas masked hypertension is normal BP in the clinic but higher BP at home.^{2,3} These measurements are more than statistical curiosities because patients with white-coat hypertension have a relatively benign prognosis. In contrast, those with masked hypertension have increased cardiovascular events compared with those with persistent normotension. The purpose of this review is to evaluate the relationship of cardiovascular events with ambulatory BP recordings in patients with chronic kidney disease (CKD).

Hypertension has a strong, graded, and linear

Indiana University School of Medicine and Richard L. Roudebush VA Medical Center, Indianapolis, IN

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Address reprint requests to Rajiv Agarwal, MD, Professor of Medicine, Division of Nephrology, Department of Medicine, Indiana University and RLR VA Medical Center, 1481 West 10th St, 111N, Indianapolis, IN 46202.

E-mail: ragarwal@iupui.edu

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relationship with cardiovascular outcomes. In the million people meta-analysis the BP value associated with the least cardiovascular risk, even among the very old, was 115/75 mm Hg.⁴ A single BP reading of 110/70 mm Hg, or a usual BP value of 115/75 mm Hg, has the lowest vascular mortality risk even among octogenarians, and there was no evidence for a J-curve in this population.⁴ Thus, optimal BP is defined as less than 120/80 mm Hg. Prehypertension is defined as 120 to 139/80 to 89 mm Hg and hypertension is defined as 140/90 mm Hg or greater.⁵ In patients with diabetes mellitus or those with CKD, the cardiovascular risk is increased to a substantial level at a BP of 130/80 mm Hg, therefore patients with these conditions are considered hypertensive at 130/80 mm Hg.⁵ What is evident from the data is the inherent relationship of a given level of BP and cardiovascular event rate. Thus, in higher-risk patients even a lower BP confers a greater cardiovascular risk compared with higher BP.

BP MISCLASSIFICATION IN CKD

Hypertension control rates among patients with CKD are dismal. The control rates of hypertension depend on the technique of BP measurement. Among patients with CKD, although 75% were treated with BP medications, 14% reached the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VI goal of lower than 130/85 mm Hg, and 36% reached a goal of lower than 140/90 mm Hg when BPs were obtained in the clinic. Overall, 11% with CKD reached the Joint National Committee VI goal (<130/85 mm Hg) and 27% reached 140/90 mm Hg.⁶

To illustrate the notion that BP control rates depend on how BP is measured, consider a study performed in 232 patients (20% black; 4% female; mean age, 67 y; 35% diabetic) with CKD who underwent a single 24-hour ambulatory BP monitoring and concomitant recording of BP in the clinic and at home for 1 week.⁷ Hypertension was defined as a systolic BP of 130 mm Hg or higher, or a diastolic BP of 80 mm Hg or higher on average awake 24-hour ambulatory BP monitoring. In this sample of veterans with CKD, systolic hypertension—with or without concomitant diastolic hypertension—was seen

in 62% of the patients, whereas isolated diastolic hypertension was seen in only 3%. The low prevalence of isolated diastolic hypertension is what has been reported previously in hemodialysis patients.⁸ Although 70% of patients had diastolic BP within the recommended levels, only 38% had well-controlled systolic BP when judged by ambulatory BP monitoring. Therefore, attention should be focused on control of systolic BP in patients with CKD. Adequate systolic BP control (<130 mm Hg) was seen in 19% to 28% of CKD patients when clinic BPs were used to assess control. However, using ambulatory BP monitoring, BP control was seen in 38% (which still is dismal).

The phenomenon of white-coat hypertension, reported in 20% to 35% of patients with essential hypertension,⁵ is more pronounced when BP is measured by a physician than by a technician,⁹ and is less prevalent when co-existing target organ damage is present.¹⁰ Clinic BPs—even when obtained by standardized technique—were misleading in a large proportion of patients with CKD. In these patients there was a high prevalence (28%-30%) of white-coat hypertension when assessed by clinic systolic BP, but there was somewhat less of an effect (24%) when assessed by systolic home BP monitoring. The Seventh Joint National Committee recommends the use of home BP monitoring before considering ambulatory BP monitoring to assess the value of clinic BPs.⁵ The goal of home BP monitoring would be to reduce the white-coat effect. We found that the white-coat effect is at least as common in patients with CKD as in those with essential hypertension, and the white-coat effect is not attenuated significantly even with home BP monitoring.

More importantly, in 26% to 34% of CKD patients the clinic systolic BP was normal, but the ambulatory BP was hypertensive, which has been called *masked hypertension*. In contrast, if systolic BP was found to be normal at home, only 13% were found to be hypertensive by ambulatory BP. Bobrie et al¹¹ reported that in elderly patients with masked essential hypertension, the cardiovascular event rate was similar to that found in the hypertensive popula-

tion. If these results are extrapolated to patients with CKD, it would be important to identify and treat as many as a third of patients with masked hypertension according to clinic BP measurements. The prognostic impact of these findings is discussed in the subsequent sections.

AMBULATORY BP MONITORING AND END-STAGE RENAL DISEASE OUTCOMES IN CKD

Timio et al¹² performed a 3-year longitudinal case-control study in 48 hypertensive patients with CKD divided into dippers ($n = 20$) and nondippers ($n = 28$). They were among the first to report that nondippers had a faster rate of decrease in creatinine clearance than the dippers (0.37 ± 0.26 versus 0.27 ± 0.09 mL/min/mo; $P = .002$). The nondippers also had a greater increase in urinary protein excretion rate than dippers (993 ± 438 versus 691 ± 222 mg/24 h; $P = .009$). This longitudinal study suggests that the nondipping pattern of ambulatory BP can be associated with a faster progression of CKD. However, hard outcomes were not measured and the study had a small number of subjects.

To test the use of ambulatory BP monitoring over clinic BP monitoring to predict renal outcomes, Agarwal and Andersen¹³ performed a longitudinal cohort study of 217 veterans with CKD. The 24-hour ambulatory BP was $133.5 \pm 16.6/73.1 \pm 11.1$ mm Hg and the clinic BP was $155.2 \pm 25.6/84.7 \pm 14.2$ mm Hg. The composite renal end point of end-stage renal disease (ESRD) or death over a median follow-up period of 3.5 years occurred in 75 patients (34.5%), death occurred in 52 patients (24.0%), and ESRD occurred in 36 of 178 patients (20.2%). Thirty-nine patients died before reaching ESRD. The ambulatory BP measurement appeared to provide greater prognostic information compared with the clinic blood pressure measurement. A 1-SD increase in the systolic BP measurement increased the risk of composite outcome by 1.69 (95% confidence interval [CI], 1.32-2.17) for the standard clinic measurement, and by 1.88 (95% CI, 1.48-2.39) for the 24-hour ambulatory BP recording. The results of this

prospective cohort study showed that, after adjustment for the clinic BP measurement, the 24-hour ambulatory systolic BP measurement provided additional prognostic information concerning ESRD and the composite end point of ESRD and death. A 1-SD increase in the 24-hour ambulatory systolic BP measurement increased the risk of ESRD by 3.04 (95% CI, 2.13-4.35), and by 2.20 (95% CI, 1.43-3.39) when adjusted for standard clinic systolic BP. Among the components of the end points that were studied, the strongest relationship emerged between systolic BP and ESRD, compared with all-cause mortality or the composite end point. Although day ambulatory BP was a stronger predictor of ESRD, night ambulatory BP was a stronger predictor of all-cause mortality and the composite renal end point.

Dipping added to the prognostic importance of ambulatory BP monitoring in predicting ESRD or deaths in our study, even after adjusting for 24-hour ambulatory systolic BP. Dipping in patients with CKD is associated with younger age, better glomerular filtration rate (GFR), lower proteinuria, and higher serum albumin concentration.¹⁴ These risk factors also are associated with the progression of kidney disease. We found that adjustment for other risk factors for CKD progression removes the independent prognostic value of ambulatory BP. Thus, it is unclear whether nondipping is an independent risk factor or simply a marker of more severe kidney disease.

In a retrospective cohort study of 322 patients with and without CKD, Davidson et al¹⁵ reported a greater decrease in estimated GFR in nondippers compared with dippers during a median follow-up period of 3.2 years. The mean change in 137 dippers in the estimated GFR was 1.3%, whereas the mean change in 185 nondippers was -15.9% ($P < .001$ for difference). The differences in the GFR decrease remained after adjusting for other risk factors. Notably, no information on proteinuria was provided. Because nondipping and CKD progression both are linked strongly to proteinuria, whether nondipping is truly an independent marker of progression remains open to question.

AMBULATORY BP AND CARDIOVASCULAR OUTCOMES IN CKD

To assess the role of out-of-clinic BP recordings in predicting cardiovascular events in patients with CKD, a prospective cohort study was conducted in 217 veterans with CKD.¹⁶ The cohort of patients had been reported previously for ESRD and mortality outcomes as mentioned above.¹³ The results of this prospective cohort study showed that, after adjustment for clinic BP, 24-hour ambulatory systolic BP provided additional prognostic information concerning the composite cardiovascular end point of myocardial infarction, stroke, and death. A 1-SD increase in systolic BP increased the hazard ratio of the composite end point by 1.16 (95% CI, 0.89-1.50) for routine BP, by 1.57 (95% CI, 1.19-2.09) for standardized BP, by 1.66 (95% CI, 1.27-2.17) for home BP, and by 1.42 (95% CI, 1.10-1.84) for 24-hour ambulatory BP recording. The hazard ratio of the composite end point was significant only for hypertension, as defined by the 24-hour ambulatory BP monitoring (hazard ratio, 2.22; 95% CI, 1.23-4.01). Only hypertension as defined by 24-hour ambulatory BP was predictive of cardiovascular outcomes, whereas definitions based on clinic or home monitoring were not. Awake and asleep BP measurements were similar in predicting outcomes, and dipping did not add to the diagnostic importance of ambulatory BP monitoring in our study. Nondipping was associated with increased cardiovascular risk, but not when adjusted for other risk factors. When adjusted for risk factors for cardiovascular outcomes (by propensity score analysis), even 24-hour ambulatory BP monitoring was not associated independently with cardiovascular outcomes. Thus, factors that increase BP such as severity of kidney disease may mediate the risk that is measured through BP.

Several investigators have reported the cardiovascular risk associated with ambulatory BP monitoring in patients with ESRD. For example, in 80 patients on chronic hemodialysis, Liu et al¹⁷ showed that nondipping was associated with a hazard ratio of 2.5 for cardiovascular events and 9.6 for cardiovascular death. Tripepi et al¹⁸ showed that in hemodialysis patients without diabetes mellitus and cardiovascular

events, the night/day ratio was a predictor of total mortality and cardiovascular mortality. Interestingly, we found daytime BP to be a stronger predictor of ESRD, whereas the night systolic BP was a stronger predictor of death. Amar et al¹⁹ reported that nocturnal BP was linked to mortality in French hemodialysis patients.

Ambulatory BP monitoring requires inflation of an arm cuff at prespecified intervals to obtain a BP recording, which can disturb sleep. If sleep is disturbed then dipping may not be seen. Verdecchia et al²⁰ asked their patients if perceived sleep was disturbed during BP monitoring. They reported that if sleep is disturbed because of ambulatory BP monitoring, then nondipping was of no prognostic significance. On the other hand, if dipping is absent and the patient slept well, it was of prognostic importance. Although the results of this study may be explained by interference with sleep, it also is possible that many of the patients who reported lack of sleep were those with CKD. Nocturia (and hence disturbed sleep) is an early feature of CKD. Previous studies have shown that nondipping is associated with greater proteinuria and lower GFR.¹⁴ Thus, these factors modulate events instead of presumed lack of sleep. Nonetheless, it would be prudent to ask subjects about the quality of their sleep during ambulatory BP monitoring and also to adjust the analyses for proteinuria and GFR in epidemiologic studies.

WHAT IS THE GOAL AMBULATORY BP IN CKD?

To determine the ambulatory BP level that is associated with optimal, normal, or hypertensive clinic BP an international collaboration of investigators led to analysis of pooled data in normal individuals and patients with essential hypertension in several countries.²¹ The investigators found that the level of 24-hour ambulatory BP associated with a cardiovascular mortality rate similar to hypertensive BP (>140/90 mm Hg) was 130/80 mm Hg. Thresholds for optimal ambulatory BP was 115/75 mm Hg for 24 hours, 120/80 mm Hg for daytime, and 100/65 mm Hg for nighttime. Rounded thresholds for normal ambulatory BP were 125/75, 130/85, and 110/70 mm Hg, respectively, and

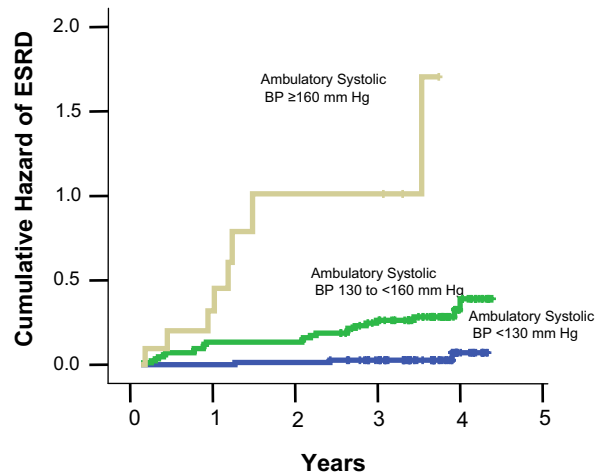


Figure 1. Cumulative risk of ESRD according to level of systolic ambulatory BP. The 24-hour ambulatory systolic BPs were divided into 3 categories: less than 130 mm Hg, 130 to less than 160 mm Hg, and 160 mm Hg or more, reflecting nationally recommended levels of control, and 2 degrees of poor control. Three of 76 (4%) patients in the well-controlled category had ESRD, 23 of 88 (26%) patients in the 130 to less than 160 mm Hg group had ESRD, and 8 of 11 (73%) in the 160 mm Hg or more category had ESRD ($P < .0001$ by log-rank test). Reprinted with permission from Agarwal and Andersen.¹³

those for ambulatory hypertension were 130/80, 140/85, and 120/70 mm Hg. The definition of hypertension in the current American Heart Association guideline is awake ambulatory BP of greater than 135/85 mm Hg. Thus, the definitions of ambulatory BP are evolving.

The level of goal ambulatory BP in patients with CKD is unknown. Because the goal BP for CKD is taken to be less than 130/80 mm Hg, which is considered a normal BP, a 24-hour ambulatory BP of less than 125/75 mm Hg, a daytime ambulatory BP of less than 130/85 mm Hg, and a nighttime ambulatory BP of less than 110/70 mm Hg would be considered reasonable goal BP targets. In patients on dialysis, it is even harder to speculate the goal ambulatory BP. However, the thresholds may be higher: less than 130/80 for 24 hours, less than 140/85 mm Hg for daytime, and less than 120/70 mm Hg for nighttime.

CONCLUSIONS

Ambulatory BP monitoring appears to be a superior prognostic marker compared with BPs

obtained in the clinic. The use of ambulatory BP monitoring results in less misclassification of BPs. Thus, ambulatory BP monitoring can identify white-coat hypertension and masked hypertension. The latter is associated with a higher risk of ESRD in patients with CKD. Ambulatory BP monitoring is a marker of cardiovascular end points in CKD. Nondipping is associated with proteinuria and lower GFR. Although nondipping is associated with more ESRD and cardiovascular events, adjustment for other risk factors removes the prognostic significance of nondipping. Thus, it is unclear whether nondipping is of independent prognostic significance. For patients with CKD, not on dialysis, it appears that a 24-hour ambulatory BP of less than 125/75 mm Hg, a daytime ambulatory BP of less than 130/85 mm Hg, and a nighttime ambulatory BP of less than 110/70 mm Hg would be considered reasonable goal BP targets.

In the management of hypertension in patients with CKD, control of hypertension is important. Ambulatory BP monitoring may be useful to assign more aggressive treatment to patients with masked hypertension and to withdraw antihypertensive therapy in patients with white-coat hypertension (Fig. 1).

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