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COMMENTARY

Ambulatory blood pressure in chronic kidney disease: do ethnic disparities exist?

Yuichiro Yano

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Global health, demographic changes (population growth and aging) and environmental destruction, including climate change and natural disasters, are the key challenges we face in the twenty-first century. In terms of global health, understanding the rates and numbers of people who die as well as where, at what age and from what diseases is a crucial step for planning interventions.[1] The Global Burden Disease Study, which was launched by the World Bank and the World Health Organization in 1991, provides a comprehensive and internally consistent source of information on the global burden of disease over time.[1] The 2010 report ranked chronic kidney disease (CKD) 18th on the list of conditions that cause the most deaths worldwide.[2] Its position jumped from 27th in 1990; only HIV/AIDS moved more positions up the list. In addition, the overall increase from 1990 to 2010 in the years of life lost because of premature mortality was the fourth largest in CKD (51%), behind HIV/AIDS (372%), stroke (177%) and diabetes mellitus (70%). Thus, CKD is now recognized as an emerging global health issue.[3]

CKD prevalence is generally increasing worldwide but varies by region (10–15%). Its clinical features also differ around the globe.[3] CKD involves not only end-stage renal disease and cardiovascular disease (CVD) but also cognitive dysfunction, psychological problems and musculoskeletal issues. These issues lead to a substantial loss of health and are costly for health-care systems to manage. Thus, the identification of individuals who are at risk for these complications, followed by appropriate management for their prevention, is clinically important.

High blood pressure (BP), which is both a cause and consequence of CKD, is a leading risk factor for cardiorenal diseases in CKD.[3] Compared with office BP (OBP) values measured by a physician or nurse, out-of-OBP values (that is, home or ambulatory BP, especially nocturnal BP), have been shown to precisely predict outcomes in CKD patients. An example is among African Americans with hypertension-related CKD who participated in the trial and cohort phases of the African American Study of Kidney (AASK) Disease: a majority of participants experienced renal events or died despite good OBP control and the use of renin–angiotensin system (RAS) blockers. One potential explanation is the presence of masked hypertension; of those with well-controlled OBP, 70% had either elevated daytime ($\geqslant$135/85 mm Hg) or nocturnal ($\geqslant$120/70 mm Hg) BP.[4] Masked hypertension is not uncommon in CKD.[5] Notably, a sleep BP increase or limited nocturnal BP dipping, rather than an awake BP increase, has been shown in CKD. Herein, we summarize evidence regarding the associations of OBP, ambulatory BP and outcomes in CKD populations (Table 1). Although there are some variations in the pattern of ambulatory BP in CKD, more than half of the populations had a high out-of-OBP and a non-dipper/reverse-dipper status at night.

In the current issue of *Hypertension Research*, Cha *et al.*[14] strengthened the evidence against the sole use of OBP. Using a nationwide database from Korea ($n = 1317$, mean age, 58 years; 63% men; all with CKD stage 2–4; and median eGFR, 48 ml min^{-1} per 1.73 m^2), they showed the BP control status based on the OBP and the ambulatory BP. All patients were treated with antihypertensive medications, and 25% had diabetic nephropathy. The majority were treated with two types of antihypertensive agents: RAS inhibitors were used in almost all cases (that is, 90%), suggesting that physicians who participated in this study conformed to the guidelines, and calcium-channel blockers were used in 56% of cases. An OBP of $<$140/90 mm Hg, a daytime BP of $<$135/85 mm Hg and a nocturnal BP of $<$120/70 mm Hg were defined as controlled BP. The nocturnal BP dipping status was defined as extreme dipper if the nocturnal fall in BP was $\geqslant$20%, as dipper if the nocturnal fall in BP was between 10 and 20%, as non-dipper if the nocturnal fall in BP was between 0 and 10%, and as reverse dipper if the nocturnal fall in BP was $<$0%. As a result, the BP classification was as follows: controlled hypertension, 19%; white-coat hypertension, 4%; masked hypertension, 34% and uncontrolled hypertension, 42%. The nocturnal BP dipping status was as follows: extreme-dipper, 15%; dipper, 33%; non-dipper, 35% and reverse dipper, 17%. A direct comparison of the data of Cha's study with those of the previous reports shown in Table 1 is not feasible, but the authors showed that more than half of CKD patients have high out-of-OBP and abnormal diurnal BP variation. One of the possible explanations for why so many patients (76%) had uncontrolled high BP is that they used, on average, fewer antihypertensive agents (approximately 2.3 agents) than patients in other reports (2.5–3.8 agents).[4,7,9,12,13] As the authors mentioned, the use of diuretics was

Dr Y Yano is at American Society of Hypertension Comprehensive Hypertension Center, Department of Medicine, University of Chicago Medicine, Chicago, IL, USA and Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan
E-mail: yyano@jichi.jp

Table 1 Evidence to show associations of OBP, ambulatory BP and outcomes in CKD populations.

Longitudinal study	*Subjects with CKD*	*BP information*	*Relevant findings*
Agarwall *et al.*[6]	US ($n=217$; 67 years; men, 96%; Whites, 79%; comorbidities, HT (92%?), DM (42%); eGFR 45 ml min^{-1} per 1.73 m^2)	High 24-h SBP, 57%; ND (including RD), 80%	Follow-up, 3.5 years. Non-dipping predicted ESRDS or deaths independently of 24-h SBP.
Minutolo *et al.*[7]	Italy ($n=436$; 65 years; men, 58%; comorbidities, HT (100%), DM (37%); eGFR, 43 ml min^{-1} per 1.73 m^2)	High daytime BP, 45%, high nocturnal BP, 57%; ED, 11%; D, 33%; ND, 43%; RD, 14%.	Follow-up, 4.2 years. Nocturnal SBP more than daytime SBP predicted cardiorenal events. Non-dipping and reverse-dipping status predicted cardiorenal events independently of 24-h BP.
Gabbai *et al.*[8]	US ($n=617$; 60 years; men, 62%; Blacks, 100%; cause, HT (100%); eGFR, 44 ml min^{-1} 1.73 m^2)	Masked HT, 26%; D (include ED), 20%, ND, 41%, RD, 39%.	Follow-up, 5 years. Both daytime and nocturnal SBP equally predicted cardiorenal events. Reverse dipper did not.
Redon *et al.*[9]	Spain ($n=79$; 57 years; men, 60%; comorbidity, HT (100%); eGFR, 29 ml min^{-1} per 1.73 m^2)	ND (including RD), 47%	Follow-up, 44 months. Nocturnal SBP but not daytime SBP or non-dipper predicted ESRDS or death.
Yano *et al.*[10]	Japan ($n=634$; 76 years; men, 37%; comorbidities, HT (100%), DM (15%); eGFR, 48 ml min^{-1} per 1.73 m^2)	High daytime BP, 67%; high nocturnal BP, 61%; ED, 18%; D, 41%; ND, 30%; reverse dipper, 11%.	Follow-up, 3 years. Nocturnal SBP (not daytime SBP) and reverse dipper predicted of stroke independently of OBP.

Cross-sectional study	*Subjects with CKD*	*Relevant findings*
Pogue *et al.*[4]	US ($n=617$; 60 years; men, 62%; Blacks, 100%; cause, HT (100%); eGFR, 44 ml min^{-1} per 1.73 m^2)	Controlled, 37%; white coat, 2%; masked, 43%; sustained HT, 18%; D (include ED), 20%; ND, 41%; RD, 39%
Iimuro *et al.*[11]	Japan ($n=1075$; 61 years; men, 63%; comorbidities, HT (90%), DM (35%); eGFR, 29 ml min^{-1} per 1.73 m^2)	Controlled, 38%, white coat, 6%, masked, 31%, sustained HT, 26%; ED; 10%, D; 37%, ND; 38%, RD; 16%
Mojón *et al.*[12]	Spain ($n=3,227$; 64 years; men, 60%; comorbidities, HT (100%), DM (36%); eGFR, 60 ml min^{-1} per 1.73 m^2)	High daytime BP, 53%; high nocturnal BP, 65%; ND (including RD), 61%.
Gorostidi *et al.*[13]	Spain ($n=5,693$; age range, 55–70 years; men, 46–74%; Comorbidities, HT (100%), DM (23–44%); eGFR range, 10–103 ml min^{-1} per 1.73 m^2); CKD included stage 1 and 2.	Controlled, 15%; white coat, 29%; masked, 7%; sustained HT, 50%; more than half of all CKD patients had high daytime or nocturnal BP.

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; D, dipper; DBP, diastolic BP; DM, diabetes; ED, extreme-dipper; eGFR, estimated glomerular filtration rate; ESRD; end-stage renal disease; HT, hypertension; ND, non-dipper; OBP, office BP; RD, reverse dipper, SBP, systolic BP.
Age and eGFR in subjects with CKD are shown as mean values. Reference 4 and 8 are derived from the African American Study of Kidney Disease and Hypertension. The definitions of dipping status are as follows: ED, nocturnal fall in BP is $\geqslant$20%; D, nocturnal fall in BP is $>$10% and $<$20%; ND, nocturnal fall in BP is $>$0% and $<$10%; and RD, nocturnal fall in BP is $<$0%. Also, most studies used the definition of high daytime BP as SBP$\geqslant$135 mm Hg or DBP$\geqslant$75 mm Hg, and high nocturnal BP as SBP$\geqslant$120 mm Hg or DBP$\geqslant$70 mm Hg. However, reference to each paper is recommended to confirm details.

relatively low (38%). In Asians, the intake of dietary sodium is high,[15] which could also contribute to BP elevation, especially when the kidney function is impaired. However, we should continue to pay close attention to kidney function when we consider diuretics as the combination therapy with RAS inhibitors and diuretics, particularly in non-obese hypertensive cases (common in Asians), provides less cardiorenal protection (and may even be harmful in some cases) than does RAS inhibitors together with calcium-channel blockers.[16] In contrast to the reports on Caucasians (30%)[13] but similar to those on Asians[11] and African Americans,[4] white-coat hypertension was uncommon in this study.[14]

Few reports have shown the clinical features of high out-of-OBP (particularly nocturnal BP) and abnormal diurnal BP variation in CKD. Of note, these BP alterations are not always proportional to the reduction in the renal function. Aging, diabetes, greater proteinuria, less physical activity and frequent nocturia have been reported to be associated with less nocturnal BP dipping in CKD.[4,11,13] In the study by Cha *et al.*,[14] diabetes nephropathy, pre-existing CVD, and greater proteinuria were most prevalent in reverse dippers. In contrast to the findings of AASK,[4] female gender and lower body mass index became more prevalent as the extent of nocturnal BP dipping decreased. Because of the cross-sectional nature of this study,[14] a cause-effect association cannot be inferred. That is, less nocturnal BP dipping in CKD may be a marker of poor health rather than a cause of it. To determine whether high nocturnal BP or abnormal diurnal BP variation in CKD is a reversible risk factor, interventional studies are required. In this point, a recent study ($n=661$; mean age, 59 years; 60% men; eGFR, 66–67 ml min^{-1} per 1.73 m^2) indicated that a progressive decrease in nocturnal systolic BP during follow-up was most significantly associated with a reduction in composite CVD in CKD patients (hazard ratio: 0.86, 95% confident interval: 0.77–0.96; $P<0.001$, for every 5-mm Hg decrease in nocturnal systolic BP), whereas decreases in daytime systolic BP were not.[17]

Other possible mechanisms of high nocturnal BP and/or less nocturnal BP dipping in CKD include high sympathetic nerve activity, sleep disturbances and expanded extracellular volume status as well as enhanced salt sensitivity.[5,18] These associations can also be applied to non-CKD. Neither Cha's study nor previous reports[4,6,7,8,9,11] compared ambulatory BP in those with CKD and without CKD; therefore, whether the pathophysiologies of nocturnal BP alterations differ in the presence of CKD remains uncertain. In addition, ethnic-based comparison data on ambulatory BP in CKD are limited. Generally, African Americans are thought to experience high nocturnal BP and less nocturnal BP dipping than Caucasians,[19]

which may be explained by genetic factors (for example, salt sensitivity, nitric oxide and natriuretic peptide) and by physiological, behavioral or environmental factors (e.g., socioeconomic status). The AASK showed a substantially high prevalence of reverse-dippers (39%) among African American CKD patients. In the future, we need to elucidate the mechanisms that give rise to ethnic disparities in nocturnal BP regulation that can lead to race-specific targets for CVD prevention. Thus, international collaborative studies in this field are warranted.

Although abnormal diurnal BP variation is frequently accompanied by high nocturnal BP, the prognostic value of each is not identical. In elderly hypertensive patients, high nocturnal systolic BP was associated with an increased risk for stroke regardless of CKD presence.[10] In contrast, a reverse-dipping pattern was associated with a higher stroke risk only in those with CKD. This point should be realized by obtaining the follow-up data for Cha's study.[14]

There are still some questions raised by Cha's study. First, as the authors mentioned, the time of the ingestion of antihypertensive agents is unknown. Although the findings are still controversial, the administration of antihypertensive agents at bedtime rather than after waking-up may be more effective in lowering nocturnal BP or restoring nocturnal BP dipping in CKD patients.[17] Second, the authors did not assess sleep quality or nocturia, which could influence nocturnal BP in CKD. Third, despite the usefulness of ambulatory BP monitoring (ABPM) for predicting outcomes in CKD, there are still some caveats associated with ABPM, such as cost, time and relative cumbersomeness. To overcome these difficulties, some newly developed, programmed home BP measurement devices that can measure nocturnal BP automatically have been developed.[18] More evidence, including cost-benefit analyses, is warranted to justify the clinical significance of ABPM in CKD patients.

CONFLICT OF INTEREST

The author declares no conflict of interest.

1 Frenk J, Moon S. Governance challenges in global health. *N Engl J Med* 2013; **368**: 936–942.
2 Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095–2128.
3 Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; **382**: 260–272.
4 Pogue V, Rahman M, Lipkowitz M, Toto R, Miller E, Faulkner M, Rostand S, Hiremath L, Sika M, Kendrick C, Hu B, Greene T, Appel L, Phillips RAAfrican American Study of Kidney Disease and Hypertension Collaborative Research Group. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. *Hypertension* 2009; **53**: 20–27.
5 Yano Y, Bakris GL. Recognition and management of masked hypertension: a review and novel approach. *J Am Soc Hypertens* 2013; **7**: 244–252.
6 Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. *Kidney Int* 2006; **69**: 1175–1180.
7 Minutolo R, Agarwal R, Borrelli S, Chiodini P, Bellizzi V, Nappi F, Cianciaruso B, Zamboli P, Conte G, Gabbai FB, De Nicola L. Prognostic role of ambulatory blood pressure measurement in patients with nondialysis chronic kidney disease. *Arch Intern Med* 2011; **171**: 1090–1098.
8 Gabbai FB, Rahman M, Hu B, Appel LJ, Charleston J, Contreras G, Faulkner ML, Hiremath L, Jamerson KA, Lea JP, Lipkowitz MS, Pogue VA, Rostand SG, Smogorzewski MJ, Wright JT, Greene T, Gassman J, Wang XPhillips RA; African American Study of Kidney Disease and Hypertension (AASK) Study Group. Relationship between ambulatory BP and clinical outcomes in patients with hypertensive CKD. *Clin J Am Soc Nephrol* 2012; **7**: 1770–1776.
9 Redon J, Plancha E, Swift PA, Pons S, Muñoz J, Martinez F. Nocturnal blood pressure and progression to end-stage renal disease or death in nondiabetic chronic kidney disease stages 3 and 4. *J Hypertens* 2010; **28**: 602–607.
10 Yano Y, Bakris GL, Matsushita K, Hoshide S, Shimada K, Kario K. Chronic kidney disease and nocturnal blood pressure associate with strokes in the elderly. *Am J Nephrol* 2013; **38**: 195–203.
11 Iimuro S, Imai E, Watanabe T, Nitta K, Akizawa T, Matsuo S, Makino H, Ohashi Y, Hishida AChronic Kidney Disease Japan Cohort Study Group. Clinical correlates of ambulatory BP monitoring among patients with CKD. *Clin J Am Soc Nephrol* 2013; **8**: 721–730.
12 Mojón A, Ayala DE, Piñeiro L, Otero A, Crespo JJ, Moyá A, Bóveda J, de Lis JP, Fernández JR, Hermida RCHygia Project Investigators. Comparison of ambulatory blood pressure parameters of hypertensive patients with and without chronic kidney disease. *Chronobiol Int* 2013; **30**: 145–158.
13 Gorostidi M, Sarafidis PA, de la Sierra A, Segura J, de la Cruz JJ, Banegas JR, Ruilope LMSpanish ABPM Registry Investigators. Differences between office and 24-hour blood pressure control in hypertensive patients with CKD: a 5,693-patient cross-sectional analysis from spain. *Am J Kidney Dis* 2013; **62**: 285–294.
14 Cha R-h, Kim S, Yoon SA, Ryu D-R, Oh JE, Han S-Y, Lee EY, Kim DK, Kim YS on behalf of the APrODiTe investigators. Association between blood pressure and target organ damage in patients with chronic kidney disease and hypertension: results of APrODiTe study. *Hypertens Res* 2014; **37**: 172–178.
15 Ueshima H, Zhang XH, Choudhury SR. Epidemiology of hypertension in China and Japan. *J Hum Hypertens* 2000; **14**: 765–769.
16 Weber MA, Jamerson K, Bakris GL, Weir MR, Zappe D, Zhang Y, Dahlof B, Velazquez EJ, Pitt B. Effects of body size and hypertension treatments on cardiovascular event rates: subanalysis of the ACCOMPLISH randomised controlled trial. *Lancet* 2013; **381**: 537–545.
17 Hermida RC, Ayala DE, Mojón A, Fernández JR. Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD. *J Am Soc Nephrol* 2011; **22**: 2313–2321.
18 Yano Y, Kario K. Nocturnal blood pressure and cardiovascular disease: a review of recent advances. *Hypertens Res* 2012; **35**: 695–701.
19 Profant J, Dimsdale JE. Race and diurnal blood pressure patterns. A review and meta-analysis. *Hypertension* 1999; **33**: 1099–1104.