

## EDITORIAL COMMENT

# Visit-to-visit blood pressure variability and risk of dementia in chronic kidney disease patients: why are blood pressure changes so important in cognitive functions?

Furkan Yavuz<sup>1</sup> and Mehmet Kanbay <sup>2</sup><sup>1</sup>Department of Medicine, Koc University School of Medicine, Istanbul, Turkey and <sup>2</sup>Department of Medicine, Division of Nephrology, Koc University School of Medicine, Istanbul, TurkeyCorrespondence to: Mehmet Kanbay; E-mail: [drkanbay@yahoo.com](mailto:drkanbay@yahoo.com), [mkanbay@ku.edu.tr](mailto:mkanbay@ku.edu.tr)**ABSTRACT**

Chronic kidney disease (CKD) is associated with cognitive functional impairment or dementia in addition to cardiovascular diseases. Aging of the population and the increasing prevalence of CKD in elderly patients are making dementia more prevalent. Blood pressure (BP) variability is an important risk factor for dementia. Although ample data link high BP variability with the risk of dementia in the general population, data on CKD patients are scarce. An observational cohort study conducted by Park *et al.*, including 103 139 patients, demonstrated a strong association between higher visit-to-visit BP variability and increased risk of dementia in CKD patients. Both higher systolic and diastolic BP variabilities were associated with any type of dementia, including Alzheimer's and vascular dementia. Physicians must be aware of BP variability when evaluating CKD patients with hypertension.

**Keywords:** Alzheimer, blood pressure variability, chronic kidney disease, dementia, hypertension

Park *et al.* [1] conducted an observational cohort study of 103 139 patients to investigate the association between visit-to-visit blood pressure (BP) variability and the risk of dementia in patients with chronic kidney disease (CKD). While BP variability is related to dementia in the general population, this study analyzed the association between BP variability and dementia in CKD patients. Higher systolic BP variability was associated with an increased risk of any type of dementia, including Alzheimer's and vascular dementia. Diastolic BP variability was also associated with a higher risk of all types of dementia (all-cause dementia) and low baseline estimated glomerular filtration rate (eGFR) levels were linked to a higher incidence of dementia. This study emphasizes the importance of assessing BP variability in

CKD patients, as it is associated with higher risks of cognitive function decline.

CKD has a negative impact on central nervous system and brain function through the contribution of factors such as metabolic disorders, accumulation of uremic toxins, oxidative stress and, in hemodialysis patients, hemodynamic factors. Cognitive functional decline or dementia is one of the important consequences of CKD [2]. Thus patients with CKD are at higher risk to develop dementia compared with the general population [3, 4]. The increasing aging of the population is leading to an increasing prevalence of dementia and CKD in elderly patients, which are projected to become the fifth- and sixth-leading global causes of death, respectively, in 2040, and the first- and second-

Received: 18.1.2022; Editorial decision: 25.1.2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

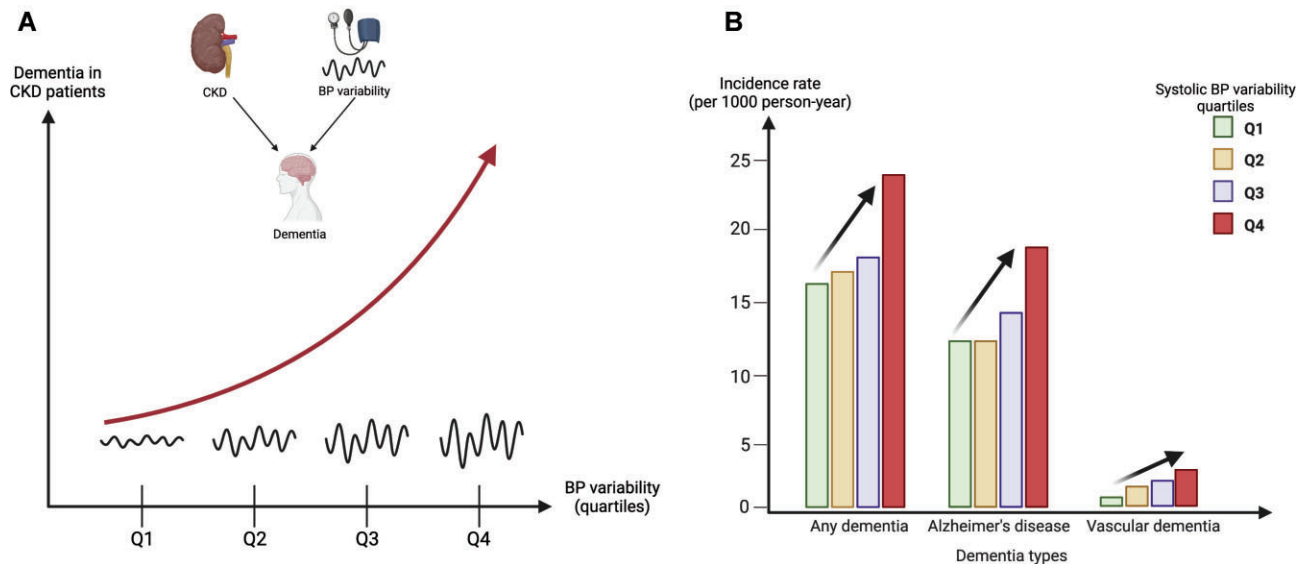


FIGURE 1: (A) Association between BP variability and incidence of dementia in CKD patients. (B) Incidence rates of dementia according to dementia types and systolic BP variability [1].

leading causes of death before the end of the century in countries with long-life expectancies [5, 6].

CKD is a common cause as well as an important complication of uncontrolled hypertension [7]. A previous clinical trial demonstrated that strict BP control in patients with or without kidney function impairment reduces the risk of dementia [8]. In addition to the presence of hypertension, variability of BP is associated with outcomes for cognitive functions.

BP variability has two main components, short-term and long-term variability, the latter being the BP recorded in the same patient in two different consecutive visits [9]. This visit-to-visit BP variability is associated with various cardiovascular, renal and neurological adverse outcomes [10, 11]. Additionally, BP variability is a significant risk factor for dementia in the general population regardless of kidney function [12]. However, studies focusing on visit-to-visit BP variability and risk of dementia in patients with CKD are thus far observational. Future studies should address whether better BP variability control may decrease the risk of dementia in CKD patients.

Park *et al.* [1] conducted a large-scale, multicenter study with multiple BP measurements and multiple variables to better assess the relationship between BP variability and dementia in 103 139 CKD patients among 11 651 753 people who underwent three or more screenings. All-cause dementia was more common in patients with higher visit-to-visit systolic BP variability [quartile (Q)1: 17.4; Q2: 17.6; Q3: 18.6 and Q4: 24.3 per 1000 person-years] and this was also the case for Alzheimer's and vascular dementia as individual entities (Figure 1A and B). The hazard ratios (HRs) for all-cause dementia in the Q4 systolic BP variability (high variability) group was 1.393 (95% confidence interval 1.309–1.483;  $P < .001$ ). A higher diastolic BP variability was also related to a higher risk of all-cause dementia and Alzheimer's disease. Thus both systolic and diastolic BP variability were risk factors for dementia.

They also confirmed that the risk of dementia was higher in patients with CKD, defined as  $eGFR < 60 \text{ mL/min/1.73 m}^2$ , in line with the current literature [13]. However, higher visit-to-visit BP variability was observed in patients who were more sedentary, currently smoking or patients with diabetes mellitus and

hypertension, which may confound or magnify the effect of BP variability [1].

Why is BP variability associated with dementia? Observational studies cannot be used to infer causality. However, there is a biologic plausibility for causality related to recurrent ischemia-reperfusion injury episodes facilitated by arterial stiffness in cerebral vessels. These pathological mechanisms are hypothesized to contribute to the development of Alzheimer's and vascular dementia [14, 15]. Therefore, physicians should be more aware of BP changes during follow-up and not focus only on one baseline BP measurement to assess the prognosis of cognitive functions.

The study by Park *et al.* [1] has some limitations. The prevalence of CKD among the source population was lower than reported previously for general populations. Furthermore, even though all centers were quality controlled, BP measurement was not standardized among centers, potentially leading to deviations from the actual measurements. Only dipstick albuminuria levels were included, due to the unavailability of quantitative measurements. Moreover, interventions to reduce BP variability were not explored and their effect on the risk of dementia was not assessed. Therefore future studies should be conducted to understand the effects of interventions to regulate BP variability on dementia.

In short, visit-to-visit BP variability is an important risk for all types of dementia, including Alzheimer's and vascular dementia, in CKD patients as in the general population. Both systolic and diastolic BP variability are associated with a higher risk of dementia. Findings of this study might be of help to design trials of optimal BP and BP variability control strategies for CKD patients with high risks of cognitive function impairment to reduce the risk of dementia. Since cognitive impairment creates a huge functional loss, physicians should not ignore this issue. Even though BP is an entity that mostly cardiologists and nephrologists are interested in, neurologists who follow dementia patients with CKD should be aware of BP variability and its negative impact on outcomes. Future studies should explore the efficacy of interventions to reduce BP variability on the risk of dementia.

## FUNDING

None.

## CONFLICT OF INTEREST STATEMENT

M.K. is a member of the CKJ editorial board. The other author has no conflict of interest to declare.

## ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

## REFERENCES

1. Park S, Cho S, Lee S et al. Association between visit-to-visit blood pressure variability and risks of dementia in CKD patients: a nationwide observational cohort study. *Clin Kidney J* 2022; <https://doi.org/10.1093/ckj/sfac020>
2. Jabbari B, Vaziri ND. The nature, consequences, and management of neurological disorders in chronic kidney disease. *Hemodial Int* 2018; 22: 150–160
3. Drew DA, Weiner DE, Sarnak MJ. Cognitive impairment in CKD: pathophysiology, management, and prevention. *Am J Kidney Dis* 2019; 74: 782–790
4. Kurella Tamura M, Xie D, Yaffe K et al. Vascular risk factors and cognitive impairment in chronic kidney disease: the Chronic Renal Insufficiency Cohort (CRIC) study. *Clin J Am Soc Nephrol* 2011; 6: 248–256
5. Foreman KJ, Marquez N, A et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *Lancet* 2018; 392: 2052–2090
6. Ortiz A, Sanchez-Nino MD, Crespo-Barrio M et al. The Spanish Society of Nephrology (SENEFRO) commentary to the Spain GBD 2016 report: keeping chronic kidney disease out of sight of health authorities will only magnify the problem. *Nefrologia (Engl Ed)* 2019; 39: 29–34
7. Hamrahian SM, Falkner B. Hypertension in chronic kidney disease. *Adv Exp Med Biol* 2017; 956: 307–325
8. Kurella Tamura M, Gaussoin SA, Pajewski NM et al. Kidney disease, intensive hypertension treatment, and risk for dementia and mild cognitive impairment: the systolic blood pressure intervention trial. *J Am Soc Nephrol* 2020; 31: 2122–2132
9. Mallamaci F, Tripepi G. Blood pressure variability in chronic kidney disease patients. *Blood Purif* 2013; 36: 58–62
10. Parati G, Torlasco C, Pengo M et al. Blood pressure variability: its relevance for cardiovascular homeostasis and cardiovascular diseases. *Hypertens Res* 2020; 43: 609–620
11. Ma Y, Song A, Viswanathan A et al. Blood pressure variability and cerebral small vessel disease: a systematic review and meta-analysis of population-based cohorts. *Stroke* 2020; 51: 82–89
12. Yoo JE, Shin DW, Han K et al. Blood pressure variability and the risk of dementia: a nationwide cohort study. *Hypertension* 2020; 75: 982–990
13. Zammit AR, Katz MJ, Bitzer M et al. Cognitive impairment and dementia in older adults with chronic kidney disease: a review. *Alzheimer Dis Assoc Disord* 2016; 30: 357–366
14. Nagai M, Dote K, Kato M et al. Visit-to-visit blood pressure variability and Alzheimer's disease: links and risks. *J Alzheimers Dis* 2017; 59: 515–526
15. Tedla YG, Yano Y, Carnethon M et al. Association between long-term blood pressure variability and 10-year progression in arterial stiffness: the multiethnic study of atherosclerosis. *Hypertension* 2017; 69: 118–127