News Release

Title

Relationship between the lower limit of systolic blood pressure target and kidney function decline in advanced chronic kidney disease: an instrumental variable analysis from the REACH-J CKD cohort study

Key Points

- In patients with chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, the instrumental variable for the lower limit of systolic blood pressure (SBP) target at ≥110 mmHg (vs. ≤100 mmHg) was associated with less eGFR decline.
- The renoprotective effect was particularly larger in the subgroups of the elderly and those with a history of cardiovascular disease.
- Because a minority of nephrologists set the lower limit of SBP target at 110 mmHg or higher, there is room to improve renal prognosis of many patients with CKD by optimizing the policies of the lower limit of SBP target based on these results.

Summary

A research group led by Shimon Kurasawa and Shoichi Maruyama of the Department of Nephrology, Nagoya University Graduate School of Medicine, has investigated the association of the lower limit of SBP target with changes in kidney function using the data from the REACH-J CKD cohort study. As a result, it was found that the lower limit of SBP target 110 mmHg or higher was associated with improving eGFR decline by 1 mL/min/1.73 m^2 per year. This study was supported by a Grant-in-Aid for Research on Advanced Chronic Kidney Disease (REACH-J), Practical Research Project for Renal Diseases from the Japan Agency for Medical Research and Development (AMED under grant numbers: JP17ek0310005 and JP20ek0310010) and conducted in collaboration with Dr. Kunihiro Yamagata (Professor, Department of Nephrology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan) and other researchers from the REACH-J CKD cohort study.

Hypertension is often comorbid with CKD, and blood pressure management is essential to preserve kidney function and prevent cardiovascular disease. While hypertension causes kidney function worsening and cardiovascular disease, excessive blood pressure lowering increases adverse events such as acute kidney injury. Patients with CKD have high blood pressure variability and are prone to excessively low blood pressure due to

intensive antihypertensive treatment. Additionally, they are susceptible to hypotension because of impaired autoregulation of blood flow and stenosis of coronary and cerebral arteries. Therefore, it is considered necessary to pay attention to the lower limit of SBP in its variability to avoid too low SBP; however, its optimal target is unclear.

The group investigated the association of the lower limit of SBP target with eGFR decline for 4 years before enrollment using data from the REACH-J CKD cohort study, which enrolled 1,320 patients with advanced CKD and collected information on patients and practice patterns of 91 nephrologists in the participating facilities. The instrumental variable for the lower limit of SBP target 110 mmHg or higher was associated with an improvement in eGFR slope of 1 mL/min/1.73 m^2 per year. This renoprotective effect was particularly larger in the subgroups of the elderly and those with a history of cardiovascular disease. The percentage of nephrologists who answered to set the lower limit of SBP target at 110 mmHg or higher was 22–36%.

These results suggest the efficacy of paying attention to the lowest SBP, specifically, 110 mmHg as the lower limit in blood pressure management of advanced CKD. It may be preferable for patients with wider SBP variations to set a higher blood pressure target to prevent hypotension.

Research Background

It is estimated that 14.8 million people in Japan have CKD, making it a national disease affecting 1 in 7 adults, and more than 40,000 patients newly initiate dialysis therapy every year. Hypertension complicates approximately 85% of patients with CKD and is an important risk factor for worsening kidney function and cardiovascular disease. Therefore, appropriate blood pressure control is essential to preserve kidney function and prevent cardiovascular disease. Recent studies have shown that intensive antihypertensive treatment reduces cardiovascular disease and mortality, while excessively low SBP is associated with an elevated risk of adverse events such as acute kidney injury.

Patients with CKD have high blood pressure variability and are prone to excessive blood pressure reduction due to intensive antihypertensive treatment based on the highest or mean value of SBP. Additionally, they are susceptible to hypotension because of impaired autoregulation of blood flow and stenosis of coronary and cerebral arteries. Therefore, it is considered necessary to pay attention to the lowest value of SBP in its variability to avoid too low SBP; however, little is known about the significance of the lower limit of SBP and its optimal target. Generally, an observational study to assess the association between the ‘actual blood pressure’ and subsequent outcomes,

such as kidney function decline and cardiovascular events, is not a sufficient basis for a policy of blood pressure management. This is because the target values for blood pressure do not always match the actual blood pressure, and the influence of various factors cannot be eliminated. Therefore, it was desirable to clarify the relationship between 'the blood pressure target' and outcomes, which is often investigated by a randomized controlled trial. However, this study evaluated the association of 'the practice policy' regarding the lower limit of SBP target with kidney function decline and cardiovascular disease using an instrumental variable method. The REACH-J CKD cohort study enrolled patients with advanced CKD and collected information on patients and nephrologists' practice patterns in the participating facilities, which made it possible to apply this analysis method.

Research Results

A total of 91 nephrologists in the 31 participating facilities answered the survey regarding the practice patterns. Answers for the questionnaire on the lower limit of SBP target were tabulated. Then, the percentage of nephrologists in each facility who answered in the survey that their lower limit of SBP target was 110 mmHg or higher was calculated. The association of this facility-level percentage with changes in eGFR for 4 years before enrollment and a history of cardiovascular disease of enrolled patients was assessed in the eligible 20 facilities where ≥50% of nephrologists answered the survey.

<u>The lower limit of SBP targets set by nephrologists</u>

Questions on SBP targets were repeated for eight possible patient groups based on a combination of kidney function (CKD stage 3 or 4–5) and diabetes and proteinuria status (non-diabetes and proteinuria-negative; non-diabetes and proteinuria <300 mg/d; non-diabetes and proteinuria ≥300 mg/d; and diabetes). Responses were obtained from 82–90 nephrologists for each. The majority answered 100 or 110 mmHg in any case of diabetes and proteinuria status or CKD stages. When the answers were dichotomized into ≥110 and ≤100 mmHg, the percentages of nephrologists who answered in the survey that their lower limit of SBP target was ≥110 mmHg were 36% for patients with proteinuria-negative without diabetes, 29% for patients with non- proteinuria <300 mg/d without diabetes, 22% for patients with proteinuria ≥300 mg/d without diabetes, and 23% for patients with diabetes. There was little difference between CKD stages 3 and 4–5.

<u>Association between the lower limit of SBP target and kidney function decline</u>

The percentage of nephrologists who answered in the survey that their lower

limit of SBP target was ≥110 mmHg was calculated for each eight possible patient group and each facility.
This facility-level proportion was considered an instrumental variable reflecting the probability that patients at that facility would receive management with the lower limit of SBP target at ≥110 mmHg. The corresponding instrumental variable was assigned to each of the 1,320 patients enrolled at the eligible 20 facilities, according to the category based on diabetes and proteinuria status and CKD stage.

In the analysis using the mixed-effects model, the mean eGFR slope ± standard deviation was -2.48 ± 2.15 mL/min/1.73 m^2 per year over the 4 years to baseline with up to five points of each year. In the multivariable analysis, the instrumental variable for the lower limit of SBP target at ≥110 mmHg was associated with less eGFR decline; the coefficient (95% confidence interval) was +1.05 (0.33–1.77) mL/min/1.73 m^2 per year. Considering the mean eGFR slope, this result suggests that the lower limit of SBP target ≥110 mmHg can slow eGFR decline by 30–40% compared with the lower limit of SBP target ≤100 mmHg. This renoprotective effect was generally consistent across the subgroups but was pronounced in subgroups of the elderly (≥75 years) and those with a history of cardiovascular disease. Patients in these groups were assumed to have more advanced atherosclerosis, making them more prone to excessively low SBP due to large SBP variations and more susceptible to hypotension. Such patients particularly need to avoid excessively low SBP.

Because these analyses evaluated the relationship between kidney function decline and 'intention' to manage the lower limit of SBP rather than the actual lowest SBP itself, the results are expected to be similar to those obtained from a randomized controlled trial.

Results of other analyses

To confirm the validity of the instrumental variable for the lower limit of SBP target ≥110 mmHg, its association with the actual lowest SBP was assessed; the instrumental variable was indeed associated with a higher value of lowest SBP. There was no association between the instrumental variable and a history of cardiovascular disease.

Research Summary and Future Perspective

The results of this study suggest the usefulness of paying attention to the lowest SBP, specifically, 110 mmHg as the lower limit in blood pressure management of advanced CKD in terms of preserving kidney function. It is considered essential for patients with wider SBP variations to set a higher blood pressure target to prevent hypotension. Because a minority of

nephrologists (22–36%) set the lower limit of SBP target at 110 mmHg or higher, there is room to improve renal prognosis of many patients with CKD by optimizing the policies of the lower limit of SBP target based on these results.

This is the first study focusing on the lower limit of SBP target, and the necessity to pay attention to the lowest SBP and to set a lower limit of SBP target may be reflected in future practice guidelines. It is hoped that future clinical trials will verify the results of this study and whether adverse events such as heart failure will increase.

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Authors: Shimon Kurasawa[1,2], Yoshinari Yasuda[1], Sawako Kato[1], Shoichi Maruyama[1], Hirokazu Okada[3], Naoki Kashihara[4], Ichiei Narita[5], Takashi Wada[6], and Kunihiro Yamagata[7]; the REACH-J CKD collaborators

Affiliations:
[1] Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[2] Department of Clinical Research Education, Nagoya University Graduate School of Medicine, Nagoya, Japan
[3] Department of Nephrology, Saitama Medical University, Saitama, Japan
[4] Department of Nephrology and Hypertension, Kawasaki Medical School, Okayama, Japan
[5] Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Science, Niigata, Japan
[6] Department of Nephrology and Laboratory Medicine, Kanazawa University, Ishikawa, Japan
[7] Department of Nephrology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

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