Intensive Blood Pressure Lowering in Patients With Renal Impairment and Lacunar Stroke

Stephen Makin, PhD; William N. Whiteley, PhD

There is a complex relationship between higher blood pressure, chronic kidney disease (CKD), and the risk of stroke. Higher blood pressure is associated with a higher risk of incident ischemic stroke and more strongly with a higher risk of incident hemorrhagic stroke.[1] Although patients with CKD are at a higher risk of stroke, there is not a consistent monotonic relationship between higher blood pressure and higher risk of cardiovascular diseases in patients with CKD; indeed, low or normal blood pressures have been associated with a higher risk of incident cardiovascular diseases in some studies. This relationship may be causal, but also could be explained by reverse causality.[2]

Patients with CKD seem to be at particularly high risk of stroke. There is an inverse linear relationship between glomerular filtration rate and the risk of stroke, with an ≈7% increased relative risk of stroke for every 10–mL/min per 1.73 m^2 decrease in glomerular filtration rate, which seems consistent across major stroke subtypes.[3]

In addition, it has been hypothesized that strokes caused by cerebral small-vessel disease ("lacunar strokes") are part of a multisystem small-vessel disorder that affects both the cerebral and the renal circulations. At younger ages, there are associations between renal impairment and cerebral white matter hyperintensities and other markers of cerebral small-vessel disease, although whether this is a manifestation of risk factors common to stroke and CKD (chiefly hypertension) or other mechanisms is uncertain.[4–6]

For these reasons, the effect of intensive blood pressure reduction on stroke incidence in patients with CKD is of particular interest for clinicians and epidemiologists.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Agarwal and colleagues[7] present a secondary analysis of data from the SPS3 (Secondary Prevention of Small Subcortical Strokes) trial, reporting the effect of intensive blood pressure reduction in patients with recent lacunar stroke with and without CKD (defining CKD as estimated glomerular filtration rate <60 mL/min per 1.73 m^2).[8] The SPS3 trial was a factorial trial that randomly allocated patients with a recent magnetic resonance imaging–defined lacunar stroke to a systolic blood pressure target of <130 mm Hg versus 130 to 149 mm Hg; and to aspirin versus aspirin and clopidogrel. An important blood pressure difference was achieved between groups at 1 year (ie, an 11–mm Hg difference in systolic blood pressure). With more intense blood pressure lowering, a modest but nonsignificant reduction in incidence of all stroke, the primary outcome, was observed (hazard ratio, 0.84; 95% CI, 0.64–1.03).

In this secondary report of the SPS3 trial, patients with CKD had a higher risk of recurrent stroke, as expected. However, there was no qualitative or statistical evidence of a difference in the formally neutral effect of intensive blood pressure lowering on death, stroke, myocardial infarction, or intracranial hemorrhage between patients with CKD and patients without CKD.

This is consistent with the results of the SPRINT (Systolic Blood Pressure Intervention Trial), which did not demonstrate a modification in the beneficial effect of intensive versus less intensive blood pressure lowering on cardiovascular outcomes in patients with and without CKD.[9] In SPRINT, intensive blood pressure lowering was also not associated with a lower quality of life. Prior neutral trials of intensive blood pressure lowering in patients with CKD may have included too few participants to detect any positive effects on myocardial infarction or stroke.[10,11]

Therefore, the present study does not support different blood pressure targets for patients with lacunar stroke with and without CKD. This is of relevance for physicians looking after patients with recent stroke. For physicians looking after patients with CKD, further trials of intense BP lowering

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Centre for Rural Health, University of Aberdeen, Glasgow, United Kingdom (S.M.); and Centre for Clinical Brain Sciences, University of Edinburgh, United Kingdom (W.N.W.).

Correspondence to: William N. Whiteley, PhD, Centre for Clinical Brain Sciences, 49 Little France Cres, Edinburgh EH16 4SB, United Kingdom. E-mail: william.whiteley@ed.ac.uk

J Am Heart Assoc. 2019;8:e013637. DOI: 10.1161/JAHA.119.013637.

© 2019 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

targeting this group have been suggested to dispel remaining clinical uncertainties about the balance between potential harms of blood pressure lowering, particularly to the kidney, and the potential benefits of blood pressure lowering, reducing incidence of myocardial infarction, stroke, and progression of renal disease.[2]

Disclosures

None.

References

1. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
2. Herrington W, Staplin N, Judge PK, Mafham M, Emberson J, Haynes R, Wheeler DC, Walker R, Tomson C, Agodoa L, Wiecek A, Lewington S, Reith CA, Landray MJ, Baigent C; SHARP Collaborative Group. Evidence for reverse causality in the association between blood pressure and cardiovascular risk in patients with chronic kidney disease. *Hypertension*. 2017;69:314.
3. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2015;30:1162–1169.
4. Makin SDJ, Cook FAB, Dennis MS, Wardlaw JM. Cerebral small vessel disease and renal function: systematic review and meta-analysis. *Cerebrovasc Dis*. 2015;39:39–52.
5. Liu B, Lau KK, Li L, Lovelock C, Liu M, Kuker W, Rothwell PM. Age-specific associations of renal impairment with magnetic resonance imaging markers of cerebral small vessel disease in transient ischemic attack and stroke. *Stroke*. 2018;49:899–904.
6. Ikeme JC, Pergola PE, Scherzer R, Shlipak MG, Catanese L, McClure LA, Benavente OR, Peralta CA. Cerebral white matter hyperintensities, kidney function decline, and recurrent stroke after intensive blood pressure lowering: results from the Secondary Prevention of Small Subcortical Strokes (SPS3) trial. *J Am Heart Assoc*. 2019;8:e010091. DOI: 10.1161/JAHA.118.010091.
7. Agarwal A, Cheung AK, Ma J, Cho M, Li M. Effect of baseline kidney function on the risk of recurrent stroke and on effects of intensive blood pressure control in patients with prior lacunar stroke: a post hoc analysis of the SPS3 Trial (Secondary Prevention of Small Subcortical Strokes). *J Am Heart Assoc*. 2019;8:e013098. DOI: 10.1161/JAHA.119.013098.
8. The SPS3 Investigators. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med*. 2012;367:817–825.
9. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, Cushman WC, Hawfield AT, Johnson KC, Lewis CE, Oparil S, Rocco MV, Sink KM, Whelton PK, Wright JT Jr, Basile J, Beddhu S, Bhatt U, Chang TI, Chertow GM, Chonchol M, Freedman B, Haley W, Ix JH, Katz LA, Killeen AA, Papademetriou V, Ricardo AC, Servilla K, Wall B, Wolfgram D, Yee J; SPRINT Research Group. Effects of intensive BP control in CKD. *J Am Soc Nephrol*. 2017;28:2812–2823.
10. Appel LJ, Wright JT, Greene T, Agodoa LY, Astor BC, Bakris GL, Cleveland WH, Charleston J, Contreras G, Faulkner ML, Gabbai FB, Gassman JJ, Hebert LA, Jamerson KA, Kopple JD, Kusek JW, Lash JP, Lea JP, Lewis JB, Lipkowitz MS, Massry SG, Miller ER, Norris K, Phillips RA, Pogue VA, Randall OS, Rostand SG, Smogorzewski MJ, Toto RD, Wang X; AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med*. 2010;363:918–929.
11. Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, Lesti M, Perticucci E, Chakarski IN, Leonardis D, Garini G, Sessa A, Basile C, Alpa M, Scanziani R, Sorba G, Zoccali C, Remuzzi G; REIN-2 Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet*. 2005;365:939–946.

Key Words: Editorials • blood pressure • renal disease • stroke prevention