Impact of Intensive Blood Pressure Lowering on Management Strategies for Cerebral Small Vessel Disease: A Postprint

Authors: Liu Ziyue, Zhu Yicheng

Date: 2019-02-25T00:00:00+00:00

Abstract

In 2017, the American College of Cardiology and the American Heart Association proposed lowering the diagnostic threshold for hypertension to 130/80 mmHg (1 mmHg = 0.133 kPa), which differs from other guidelines. The fundamental goal of antihypertensive therapy is target organ protection. In recent years, issues related to antihypertensive therapy and the prevention of cerebral small vessel disease have garnered increasing clinical attention. Current research findings suggest that antihypertensive therapy may confer certain benefits for secondary prevention in patients with lacunar stroke and for preventing the progression of white matter lesions. However, the optimal blood pressure target remains undetermined. Blood pressure and clinical outcomes may exhibit a J-curve relationship, where both excessively low and high blood pressure may be harmful, and the blood pressure target that yields maximal benefit remains to be further explored.

Full Text

1. Correlation Between Hypertension and Imaging Markers of Cerebral Small Vessel Disease

Cerebral small vessel disease affects intracranial small arteries, arterioles, capillaries, and venules [4], with diagnosis primarily dependent on magnetic resonance imaging (MRI). Characteristic imaging manifestations include recent small subcortical infarcts, white matter hyperintensities (WMH), cerebral microbleeds, perivascular spaces, and brain atrophy [5]. Cross-sectional studies have demonstrated a correlation between blood pressure and the imaging burden of cerebral small vessel disease [6-10].

A recent Japanese study of 8,167 neurologically healthy adults from the Kashima Scan Study found that each 10 mmHg increase in 24-hour ambulatory systolic

blood pressure was associated with a 1.25-fold (95% CI: 1.02-1.52) higher risk of increased total cerebral small vessel disease burden score, while each 5 mmHg increase in diastolic blood pressure conferred a 1.32-fold (95% CI: 1.12-1.56) higher risk [6]. The total small vessel disease burden was defined as a composite score (0-4) assigned for the presence of vascular-origin lacunes, WMH, perivascular spaces, or microbleeds, with higher scores indicating greater burden. Another study indicated that non-dipper or reverse-dipper patterns of nocturnal ambulatory blood pressure may predict lacunar infarction in patients with essential hypertension [13].

In the Rotterdam Study of 12,467 individuals, midlife vascular risk factor exposure accelerated structural brain aging and cognitive decline [9]. A longitudinal follow-up study found that both increases and decreases in blood pressure compared to baseline were associated with subcortical white matter lesion progression, suggesting a J-shaped relationship [10]. The inflection point of this J-curve relationship was identified at 124/67 mmHg, indicating that both elevated and reduced systolic pressure may be harmful. Research has also shown that increased blood pressure variability is independently associated with cerebral small vessel disease, and that ambulatory blood pressure monitoring demonstrates stronger correlations with small vessel disease than office-based measurements [11].

2. Protective Effects of Antihypertensive Therapy on Cerebral Small Vessels

Over the past several years, the National Institutes of Health has supported three major randomized clinical trials to determine whether blood pressure targets lower than conventionally recommended provide greater protection against cardiovascular disease and stroke: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [14], the Systolic Blood Pressure Intervention Trial (SPRINT) [15], and the Secondary Prevention of Small Subcortical Strokes (SPS3) trial [16].

The SPS3 trial, a global multicenter randomized double-blind study published in *The Lancet* in 2013, enrolled patients with lacunar stroke or transient ischemic attack within the preceding 180 days. Participants were randomized to standard blood pressure control (systolic BP 130-149 mmHg) or intensive control (systolic BP <130 mmHg). Although the intensive group showed lower annual stroke recurrence rates (HR=0.81, 95% CI: 0.64-1.03), this difference did not reach statistical significance (P=0.08). Neither all-cause mortality nor treatment-related adverse events differed significantly between groups [17].

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) demonstrated that antihypertensive treatment with perindopril and indapamide significantly reduced stroke events compared to placebo in patients with cerebrovascular disease history. Subgroup analysis revealed more pronounced reductions in new white matter lesions (difference of 2.0 mm^3, P=0.012) and

total brain atrophy progression in the active treatment group [20]. The Study on Cognition and Prognosis in the Elderly (SCOPE) randomized elderly hypertensive patients to candesartan cilexetil (an angiotensin receptor blocker) or placebo, finding that the candesartan group had less WMH progression and brain atrophy, suggesting protective effects of angiotensin receptor blockers [21].

However, other studies have raised questions. The ACCORD-MIND study randomized patients with type 2 diabetes and cognitive decline to intensive (systolic BP <120 mmHg) versus standard (<140 mmHg) control. After 40 months, no significant differences in cognitive outcomes were observed, though brain imaging showed greater total brain volume decline in the intensive group (-1.86 cm^3 vs -1.61 cm^3, P=0.01) [22]. The INFINITY trial, a prospective randomized parallel-group study initiated in 2010, used 24-hour ambulatory BP targets (<130 mmHg for intensive vs <145 mmHg for standard control) in elderly patients. After 3 years, the intensive group showed more pronounced total brain volume decline without significant differences in cognitive testing [19].

3. Safety Concerns of Intensive Blood Pressure Lowering

The safety of intensive blood pressure lowering regimens remains concerning. Multiple reports have associated aggressive antihypertensive therapy with increased adverse events, including orthostatic hypotension and falls [23]. The INFINITY trial, the first intervention study to use ambulatory BP targets, has not yet published its final results, raising questions about the applicability of intensive regimens in elderly populations.

The PROFESS trial randomized 20,332 patients with prior ischemic stroke to telmisartan or placebo, subsequently classifying them by achieved blood pressure levels: normal-low (<120 mmHg), high-normal (120-<130 mmHg), normal (130-<140 mmHg), and high (150 mmHg). Results showed increased risks of recurrent stroke (HR=1.31, 95% CI: 1.13-1.52), myocardial infarction, and vascular death in the normal-low group [24]. An observational study of over 3,000 recent ischemic stroke patients also found higher recurrence rates with low-normal blood pressure (<120 mmHg) [25]. A recent blood pressure response pattern analysis from the SPS3 trial demonstrated that higher baseline BP and excessive BP reduction were associated with more adverse events [26]. Additional recognized risk factors for intensive BP lowering complications include advanced age, frailty, prior severe falls, and cognitive impairment.

4. Summary and Outlook

The correlation between hypertension and cerebral small vessel disease imaging markers is well-established, forming the foundation for antihypertensive therapy in secondary prevention. Current evidence suggests that more intensive blood pressure control may benefit secondary prevention of lacunar stroke and slow WMH progression, though the optimal target remains undefined. Multiple stud-

ies indicate a J-curve relationship between blood pressure and clinical outcomes, where both excessively low and high pressures may be harmful, and the nadir for maximal benefit requires further investigation.

The safety of intensive regimens remains unconfirmed, particularly regarding applicability in elderly populations. Future research should focus on identifying blood pressure targets that maximize benefits across different age strata and developing individualized treatment recommendations. Additional intervention studies are needed to provide evidence-based guidance for personalized management of cerebral small vessel disease in secondary prevention settings.

References

[1] Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018;138:e426-e483.

[2] James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-520.

[3] Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *J Hypertens*. 2018;36:1953-2041.

[5] Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822-838.

[6] Yakushiji Y, Charidimou A, Noguchi T, et al. Total Small Vessel Disease Score in Neurologically Healthy Japanese Adults in the Kashima Scan Study. *Intern Med*. 2018;57:189-196.

[7] Heye AK, Thrippleton MJ, Chappell FM, et al. Blood pressure and sodium: Association with MRI markers in cerebral small vessel disease. *J Cereb Blood Flow Metab*. 2016;36:264-274.

[8] Verhaaren BF, Vernooij MW, de Boer R, et al. High blood pressure and cerebral white matter lesion progression in the general population. *Hypertension*. 2013;61:1354-1359.

[9] Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011;77:461-468.

[10] de Leeuw FE, de Groot JC, Oudkerk M, et al. A Follow-Up Study of Blood Pressure and Cerebral White Matter Lesions. *Ann Neurol*. 1999;46:827-833.

[11] Campbell P, Ghuman N, Wakefield D, et al. Long-term reproducibility of ambulatory blood pressure is superior to office blood pressure in the very elderly. *J Hum Hypertens*. 2010;24:749-754.

[13] Yan B, Peng L, Dong Q, et al. Reverse-dipper pattern of blood pressure may predict lacunar infarction in patients with essential hypertension. *Eur J Neurol*. 2015;22:1022-1025.

[14] ACCORD Study Group, Cushman WC, Evans GW, et al. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. *N Engl J Med*. 2010;362:1575-1585.

[15] SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373:2103-2116.

[16] Investigators TS. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet*. 2013;382:507-515.

[17] Hart RG, Pearce LA, Bakheet MF, et al. Predictors of stroke recurrence in patients with recent lacunar stroke and response to interventions according to risk status: secondary prevention of small subcortical strokes trial. *J Stroke Cerebrovasc Dis*. 2014;23:618-624.

[18] Odden MC, McClure LA, Sawaya BP, et al. Achieved Blood Pressure and Outcomes in the Secondary Prevention of Small Subcortical Strokes Trial. *Hypertension*. 2016;67:63-69.

[19] White WB, Marfia R, Schmidt J, et al. INtensive versus standard ambulatory blood pressure lowering to prevent functional decline in the elderly (INFINITY). *Am Heart J*. 2013;165:258-265, e251.

[20] Dufouil C, Chalmers J, Coskun O, et al. Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS MRI Substudy. *Circulation*. 2005;112:1644-1650.

[21] Firbank MJ, Wiseman RM, Burton EJ, et al. Brain atrophy and white matter hyperintensity change in older adults and relationship to blood pressure. Brain atrophy, WMH change and blood pressure. *J Neurol*. 2007;254:713-721.

[22] Williamson JD, Launer LJ, Bryan RN, et al. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. *JAMA Intern Med*. 2014;174:324-333.

[23] Supiano MA. Benefit-based approach to blood pressure control in older adults. *J Am Geriatr Soc*. 2015;63:730-732.

[24] Ovbiagele B, Diener HC, Yusuf S, et al. Level of Systolic Blood Pressure Within the Normal Range and Risk of Recurrent Stroke. *JAMA*. 2011;306:2137-2144.

[25] Ovbiagele B. Low-normal systolic blood pressure secondary stroke risk. *J Stroke Cerebrovasc Dis*. 2013;22:633-638.

[26] Ku E, Scherzer R, Odden MC, et al. Patterns of blood pressure response during intensive BP lowering and clinical events: results from the secondary prevention of small subcortical strokes trial. *Blood Press*. 2017;27:73-81.

Note: Figure translations are in progress. See original paper for figures.