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REVIEW PAPER

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Effect of intensive blood pressure control on the prevention of white matter hyperintensity: Systematic review and meta-analysis of randomized trials

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Abstract

Hypertension is an important cause of cerebral small vessel disease, especially of white matter hyperintensity (WMH). The ability of intensive blood pressure (BP) control in preventing this pathological progression remains unclear. The authors systematically searched PubMed, EMBASE, SCOPUS, and Cochrane library for publications until July 20, 2020. Studies included were clinical trials with random allocation to an antihypertensive medication against placebo, or different treatment targets. The primary outcome was intergroup differences in the change of WMH volume. A random-effect model was applied for pooling effect measures. Subgroup analysis and meta-regression were conducted to explore heterogeneity. Seven studies with 2693 patients were identified. Compared with the control group, patients in the intensive BP control group had a slower progression of WMH, with a pooled intergroup standard mean difference (SMD) for WMH change of −0.22 (95% CI: −0.35 ~ −0.09, $I^2 = 63\%$). For studies comparing intensive and standard BP target, the pooled SMD is −0.37 (95% CI:-0.50~-0.24, $I^2 = 0\%$), while the pooled SMD of studies comparing active antihypertensive medication and placebo was only −0.08 (95% CI: −0.17 ~ 0.01, $I^2 = 0\%$). Meta-regression analysis showed that the reduction in WMH progression is proportional to the magnitude of intensive BP control ($\beta = -0.028$, $P < .001$). In conclusion, intensive BP control prevents WMH progression, and its effect is associated with the magnitude of intensive BP control.

1 | INTRODUCTION

Cerebral small vessel disease (CSVD) is very common among human populations, especially among the elderly and those with vascular risk factors. CSVD is an important cause of dementia and stroke[1]; it is often ignored in clinical practice due to its insidious process of progression. White matter hyperintensity (WMH) is one of the most important MRI marker of CSVD. It is associated with higher risk of stroke, cognitive decline, dementia, and death and therefore is commonly used as a surrogate end point for brain health in research settings.[2] Adjustment of modifiable risk factors is the priority in the treatment of CSVD.[3]

Hypertension is the leading risk factor of WMH.[4,5] Even stage 1 hypertension (SBP 130-139 mm Hg or DBP 80-89 mm Hg) is associated with accelerated WMH progression.[6] Meanwhile, the relative risk of WMH progression depends on the duration of hypertension and quality of blood pressure (BP) management.[7] Therefore, BP control is crucial

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for the prevention of WMH. Despite the presence of a few conflicting voice, in recent years, emerging evidence has shown the benefit of more intensive BP control in terms of cerebrovascular events and WMH.[8-14]

In the present study, we systematically reviewed randomized trials investigating the effect of intensive BP control on the prevention of WMH progression.

2 | METHODS

2.1 | Searching strategy

This systematic review and meta-analysis were conducted under the guidance of Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Appendix Table S1). And the protocol has been registered on the PROSPERO (CRD42020184962). We systematically searched PubMed, EMBASE, SCOPUS, and Cochrane Central Register of Controlled Trials for publications until July 20, 2020. The search was performed by two authors independently (YW-L and C-J). The detailed electronic searching strategy was shown in Appendix Table S2 in the supplement. The references of relevant articles were also reviewed.

2.2 | Inclusion criteria and study selection

Eligible studies should be clinical trials enrolling adults with hypertension or other vascular risk factors including elderly, diabetes, stroke or TIA, and cardiovascular diseases. The study population should be randomly allocated to an antihypertensive medication against placebo on the basis of background antihypertensive therapy, or different treatment targets. Meanwhile, eligible studies should include baseline and follow-up MRI assessment of white matter lesions. Inclusion was restricted to trials reported in English.

Two authors (YW-L and C-J) independently reviewed all the retrieved titles and abstracts for eligible studies. The full text of eligible studies was further acquired and reviewed.

2.3 | Data extraction and quality assessment

Two authors independently reviewed the full text of eligible studies to extract necessary data and assess their quality. Baseline characteristics of studies including date of publication, sample size, duration of follow-up, mean age of population, baseline SBP, antihypertensive medications, or BP goals were documented. SBP achieved after the intervention and the SBP change was also assessed; differences in achieved SBPs between intervention and control group were also calculated to describe the magnitude of intensive BP control. The outcome was defined as changes of total WMH volume from baseline to the last MRI scanning.

The quality of studies was assessed using Cochrane Collaboration's tool for assessing risk of bias. A third author (X-D) was involved in the discussion if there was any disagreement on the quality of the study.

2.4 | Data synthesis and statistical analysis

Continuous variables are presented as mean (SD) or median (range); categorical variables are presented as numbers (frequency). Effect size of outcome is presented as standard mean difference of WML changes between intensive and control group. Random-effect model was used for pooling the effect measures, and the result for fixed-effect model was also provided to illustrate the robustness of the pooled effect. Forest plots were used to summarize individual and pooled effect measures of the studies. Both funnel plot and Egger's linear regression were applied to assess publication bias.

Heterogeneity was investigated using I-square test. Further, the subgroup analysis was conducted in studies comparing intensive and standard BP target as well as studies comparing active antihypertensive medication and placebo. The Meta-regression was also conducted to further explore the relation between the effect measure and mean age of population, duration of follow-up and magnitude of SBP control. One-study-omitted sensitivity analysis was conducted to investigate the robustness of the meta-analysis.

Statistical analysis was performed in the R software. A 2-sided $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the studies

The flow diagram of literature search and review is shown in Figure 1. Among 1408 initially retrieved items, 181 were excluded due to duplication. After review of titles and abstracts, 1227 was further excluded. In the end, 23 studies underwent full-text evaluation, of which seven met the inclusion criteria.

Characteristics of eligible studies are shown in Table 1. A total of 2693 participants were enrolled from the 7 eligible RCTs, with a median age of 67.1 years (range: 60.8-80.6 years). Among them, 2314 (85.9%) had diagnosed hypertension at baseline. Three studies (INFINITY, SCOPE, and Zhang (2018)) focused on elderly hypertensive patients, two (PROGRESS and PRoFESS) enrolled patients with history of stroke, one (ACCORD MIND) enrolled patients with diabetes, and one (SPRINT MIND) enrolled patients at high risk of cardiovascular disease. Three studies compared patients with different SBP goals, and the other four compared an active hypertensive medication with placebo on the top of background treatment. The median follow-up was 36 months (range: 23.7-60). During the study period, SBP in control groups was all controlled at a reasonable level. And interventions further reduced SBP by a median of 9.1 mm Hg (range: 2.5-14.9 mm Hg). One study (PROFESS) failed to achieve significant SBP difference between intervention and control group. Risk of bias of each study is shown in Appendix Table S3.

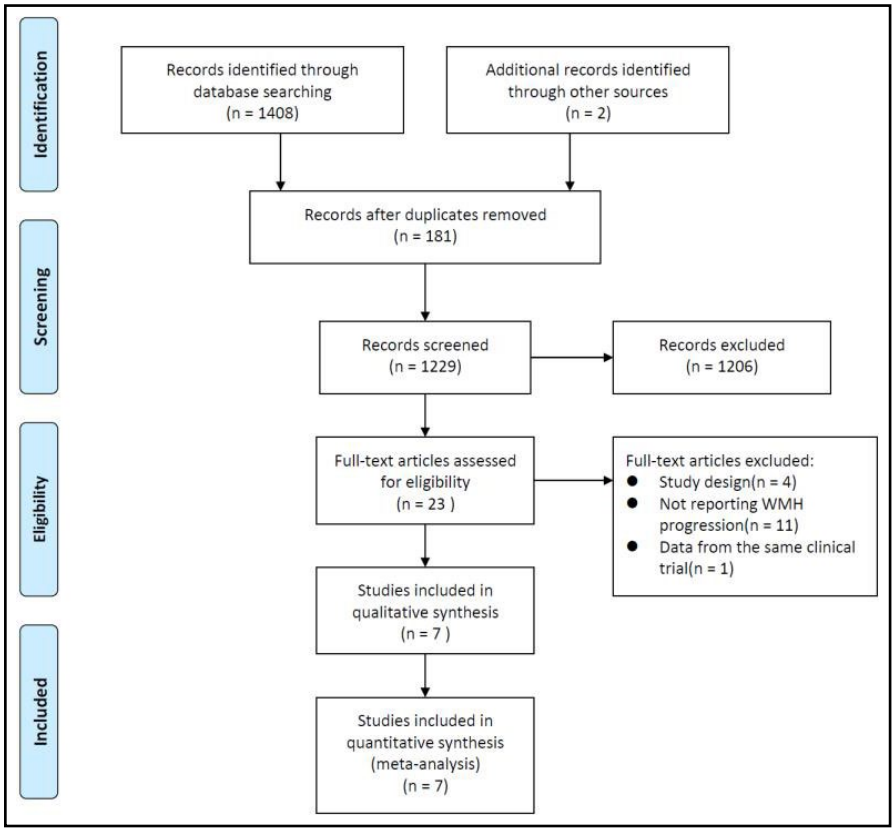

FIGURE 1 Flowchart of literature review and study selection

3.2 | Effect of intensive BP control on WML progression

The pooled standard mean difference for WML progression was −0.22 (95% CI: −0.35~-0.09) for random-effect model, with a moderate heterogeneity (I^2 = 63%). In subgroup of studies comparing intensive and standard BP goals, the pooled SMD was −0.37 (95% CI: −0.50~-0.24, I^2 = 0.0%). However, in subgroup of studies comparing active antihypertensive medication and placebo, the pooled SMD for WML progression was only −0.08 (95% CI:-0.17 ~ 0.01, I^2 = 0.0%) which narrowly missed the threshold to be statistically significant (Figure 2). Funnel plot of the eligible studies is shown in Appendix Figure S1; Egger's linear regression suggested no publication bias (P = .278).

In meta-regression, the magnitude of intensive BP control is associated with slower WML progression (β = −0.028, P < .001) (Figure 3). However, the age of the population (P = .91) and the period of follow-up (P = .65) are not associated with the effect measures.

Sensitivity analysis (Appendix Figure S2) showed that the pooled SMD remained stable with the exclusion of any one of the studies.

4 | DISCUSSION

The present systematic review provides further evidence for intensive BP control in preventing WMH progression, and a dose relation that more intensive BP control is associated with better prevention of WMH progression is also revealed.

4.1 | Clinical considerations

Hypertension results in impairment of vascular integrity including arteriosclerosis, microatheroma, and microaneurysms, which decrease cerebral blood flow and as a result cause loss of myelin and gliosis.[15,16] These pathological changes manifest on MRI as WMH.[17,18] Therefore, WMH is an important marker of hypertensive brain injury. A previous meta-analysis by Middelaar et. al. has preliminarily revealed a tendency of intensive BP control to prevent WMH progression.[19] However, only four studies were eligible at that time and the magnitude of intensive BP control was unsatisfactory in two studies (SCOPE and PRoFESS). As studies continue to emerge, the present meta-analysis further clarified this beneficial effect and confirmed the robustness of the effect through one-study-omitted sensitivity analysis.

Meanwhile, a wider range of the magnitude of intensive BP control allowed us to more reliably describe the dose relationship. Adequate magnitude of intensive BP control may be the premise of WMH prevention. In studies with prespecified antihypertensive medication, the magnitude of intensive BP control varied and is usually less intensive. The intergroup SBP difference in one study (PRoFESS) did not even achieve statistical significance. This may explain why pooled effect measure in this subgroup was not significant. In comparison, studies targeting more intensive SBP goals had

TABLE 1 Characteristics of eligible studies

Trial	Year	Sample size	Population	Age	Hypertension	Follow-up (months)	Intervention	Control	Achieved SBP	
									Intensive	Control
SPRINT MIND	2019	449	Patients ≥ 50 y with SBP 130-180 mm Hg and had increased cardiovascular risk	67.1	449 (100.0%)	48	SBP < 120 mm Hg	SBP < 140 mm Hg	120.7	134.9
ACCORD MIND	2019	314	45-79 y Diabetes patients at a high cardiovascular risk	62.3	305 (97.1%)	40	SBP < 120 mm Hg	SBP < 140mm Hg	118.6	133.5
INFINITY	2019	199	Patients > 75 y with hypertension and baseline WMH	80.6	199 (100.0%)	36	SBP < 130 mm Hg	SBP < 145mm Hg	132.6	145.6
PROGRESS	2005	192	Patients with a history of cerebrovascular disease in previous 5 y	60.8	103 (53.6%)	36	Perindopril with or without indapamide	Placebo	131.8	140.9
PRoFESS	2015	771	Patients > 50 y with recent ischemic stroke of non-cardioembolic origin	65.3	582 (75.5%)	27.6	Telmisartan	Placebo	134.9	137.4
SCOPE	2007	92	Patients at age of 70-89, with BP 160-179/90-99 mm Hg	77.0	92 (100.0%)	23.7	Candesartan	Placebo	141.0	147.0
Zhang 2018	2018	676	Community hypertensive patients aged ≥ 60 y	70.7	676 (100.0%)	60	Telmisartan	Placebo	138.8	144.0

more reliable effect of BP control and therefore prevented WMH progression to a larger extent.

4.2 | Knowledge gaps and future perspectives

Current studies also unveiled several knowledge gaps. Other MRI markers of CSVD are inadequately investigated in these studies. Of note, with 3 studies reporting the effect of intensive BP control on total brain volume, the results were conflicting. One study (SCOPE) reported less brain atrophy in active treatment group, while the other two (SPRINT MIND and ACCORD MIND) found paradoxically accelerated brain atrophy with intensive BP control. The potential cause and hazard of this phenomenon remain unclear. Previous RCTs have reported that patients receiving intensive BP control had maintained or even improved cerebral perfusion,[20,21] making it unreasonable to result in brain atrophy. However, one observational study also reported that low diastolic BP (≤70 mm Hg) is associated with more progression in subcortical brain atrophy.[22] Further studies should focus on the potential risk of hypotension, specifically low diastolic BP, during intensive BP control and its impact on CSVD and cognitive function.

Whether intensive BP control preserves cognitive function or not remains unclear. Previous RCTs failed to find significant reductions in cognitive impairment or incidence of dementia in patients receiving active antihypertensive medication.[23] The investigation of this relationship is hindered by several barriers. The incidence of dementia is quite low, meaning a large population is required for clinical trials. Moreover, cognitive screening strategies in previous studies were not sensitive enough for mild cognitive impairment. In recent studies, a battery of widely validated neuropsychological tests has been applied to assess general cognitive status and separated cognitive domains, which is able to discriminate mild cognitive impairment (MCI) and provide detailed cognitive information. MCI is a crucial stage of early intervention including risk factor management, lifestyle change, and cognitive training during cognitive decline.[24] It is closely conjoined with WMH progression in hypertensive patients. Recently, the SPRINT MIND trial has reported that intensive BP control reduced the incidence of MCI by 15%, though the effect on dementia was still not significant due to its low incidence[25] In the future, further studies on the effect of intensive BP control on mild cognitive impairment and its cause-effect relation with WMH prevention will be of great clinical importance.

5 | LIMITATION

The present meta-analysis has several limitations. Evidence has been accumulating to suggest that patients with older age, diabetes, stroke, etc, also have a high burden of WMH,[3] but the targets of intensive BP control in these patients may be different. However, due to the limited number of studies, we failed to further discuss the effect of intensive BP control on the prevention of WMH progression in specific populations like the elderly, patients with diabetes or cerebrovascular disease. Meanwhile, we did not analyze the pooled

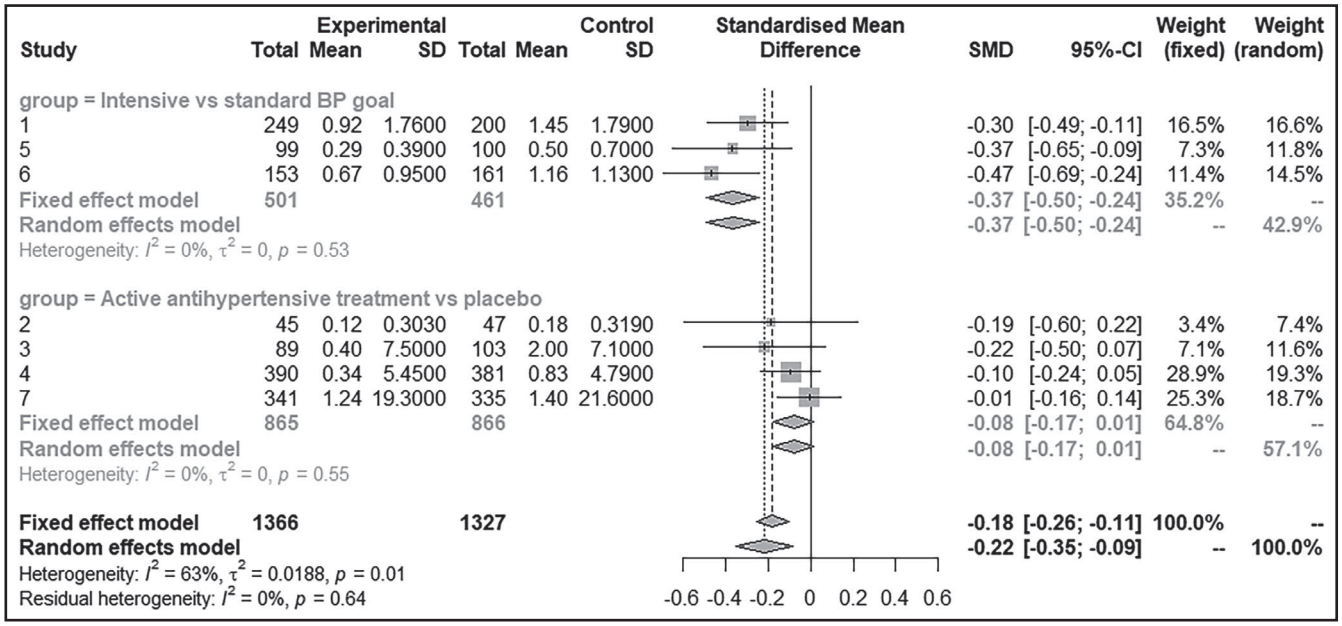

FIGURE 2 Summary of effect measures and pooled effect of intensive BP control on prevention of WMH progression

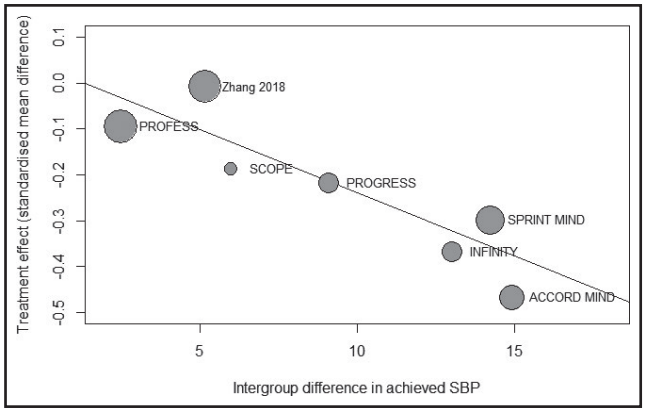

FIGURE 3 Bubble plots exhibiting the relation between the magnitude of intensive BP control and the effect measure

effect on cognitive function for the heterogeneity of cognitive scales used in these studies.

6 | CONCLUSION

In conclusion, intensive BP control significantly prevents WMH progression in patients with hypertension or other vascular risk factors. This protective effect, measured as intergroup SMD, is in proportion to the magnitude of intensive BP control. However, further studies are required to reveal the possible benefit in cognitive function, as well as the safety of intensive BP control.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

YW-L, C-J, CH-S, and CS-M are responsible for the conception and design of the systemic review and meta-analysis. YW-L and C-J systematically performed the literature searching, reviewed the retrieved items for eligibility, and evaluated the quality of eligible studies. And X-D was involved in the discussion if there was any disagreement on the eligibility and quality of the studies. YW-L and XY-G were responsible for the statistical analysis. X-D, R-B, RB-T, and JZ-D provided important advice on the methodology of meta-analysis and the data interpretation. YW-L and C-J drafted the manuscript. CH-S and CS-M critically appraised the manuscript and approved the final version. All authors have the access to all of the data, read the manuscript, and agreed to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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