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REVIEW ARTICLE

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More intensive versus conservative blood pressure lowering after endovascular therapy in stroke: a meta-analysis of randomised controlled trials

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ABSTRACT

Background: The optimum systolic blood pressure (BP) after endovascular thrombectomy for acute ischaemic stroke is uncertain. We aimed to perform an updated meta-analysis of randomised controlled trials (RCTs) to evaluate the safety and efficacy of more intensive BP management compared to less intensive BP management.

Methods: We searched various electronic databases to retrieve relevant RCTs on the clinical effects of more intensive BP management after endovascular thrombectomy compared to the less intensive management. We calculated odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes.

Results: Our meta-analysis included four RCTs with a total of 1560 patients. More intensive BP management (<140 mmHg) was associated with a statistically significant decrease in the number of patients showing functional independence (modified Rankin scale [mRS] score = 0–2) at 90 days (OR 0.69; CI = 0.51–0.94). Regarding 90-day mortality, our pooled results showed no statistically significant difference between the two groups (OR 1.21; CI = 0.89–1.65). There was no statistically significant difference between the two groups regarding the incidence of intracerebral haemorrhage (ICH) (OR 1.09; CI = 0.85–1.39) and the incidence of symptomatic intracerebral haemorrhage (sICH) (OR 1.11; CI = 0.75–1.65).

Conclusion: According to our meta-analysis, the intensive BP lowering group decreased the number of patients showing functional independence at 90 days. We found no benefit of the intensive lowering of BP on mortality rates and incidence of ICH compared to the conservative BP management. Future large-scale trials should focus on other interventions to improve prognosis in these patients.

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Meta-analysis; stroke; ischemic stroke; endovascular therapy; intensive blood pressure control

Introduction

An Acute Ischaemic Stroke (AIS) is an episode of sudden neurological dysfunction resulting from brain ischaemia, which is associated with acute infarction on brain imaging [1]. In the United States, AIS affects approximately 700,000 individuals annually and is responsible for over 150,000 deaths. AISs carry significant complications for patients, including depression, cognitive impairment and disability, in addition to placing considerable financial burdens on healthcare systems [2].

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Presently, endovascular thrombolysis (EVT) is a well-established and standard therapeutic approach for AIS resulting from a large vessel occlusion (LVO) [3]. EVT is highly effective, with successful recanalization in four out of five procedures. In early intervention EVT, for every 2–3 patients treated, one extra patient attains a reduction in disability by at least one point on the modified Rankin Scale (mRS) [4]. Favourable outcomes of EVT treatment are time-dependent: every hour delay from stroke onset to EVT initiation was linked to a 5% reduction in post-treatment functional independence. More recent trials suggest that carefully selected patients, based on initial infarct volume, have more favourable outcomes up to 24 h post-symptom onset than standard medical therapy [5,6].

Despite achieving high rates of recanalization and notable improvements in disability, the prognosis for AIS remains a challenge, as fewer than 50% of patients achieve functional independence 90 days after treatment. Interestingly, EVT procedures do not significantly reduce the incidence of mortality or risk of symptomatic intracerebral haemorrhage (sICH) [4,7].

Recent advances in newer-generation thrombectomy devices, more efficient pre-treatment admission processes, and more strict selection criteria for eligible patients have remarkably increased the efficacy and outcomes of EVT. In post-treatment care, observational studies have explored the effect of post-EVT blood pressure (BP) levels on AIS prognosis and treatment outcomes [8–13]. Optimal BP control is a challenging target, considering the adverse effects of both low and high BP. On the one hand, higher BP after EVT was associated with an increased risk of unfavourable safety outcomes in the form of sICH, mortality and requiring hemicraniectomy. BP lower than 160/90 mm/Hg was associated with better 3-month functional independence rates than permissive BP management [8,10]. On the other hand, very intensive BP lowering may compromise cerebral perfusion and increase the ischaemic core [14].

Recent guidelines recommend a BP goal of <180/105 mmHg post successful reperfusion [15]. Yet, a survey of American acute stroke centres revealed that there is no consensus on this between clinicians as most institutions do not have a standardised, post-treatment BP target. A total of 36%, 28% and 21% of institutions reported systolic blood pressure (SBP) targets of 120–139, 140–159 and ≤ 180 mmHg post-successful reperfusion, respectively [16]. For this review, we considered the BP target of <140 mmHg as intensive BP management and the BP target of 140–180 mmHg as conservative BP management.

Considering the absence of precise demonstrated guidelines and some evidence suggesting beneficial outcomes for intensive BP control, a previous meta-analysis was conducted on randomised controlled trials (RCTs) and observational studies that explored intensive BP monitoring for AIS patients post-EVT [17]. However, it suggested insignificant benefits of intensive BP control. The meta-analysis by Zhou et al. had some limitations. They mixed data from both observational studies and RCTs. The sample size was quite low. They included two RCTs and five observational studies in their analysis. Two new RCTs have recently been published on this topic [18,19]. Hence, this meta-analysis provides an updated review based on RCTs to compare and determine the efficacy of less and more intensive BP control post EVT.

Methods

This systematic review and meta-analysis, registered in Prospero with registration number CRD42023492018, was performed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [20] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [21].

Eligibility criteria

Inclusion criteria

All randomised controlled trials (RCTs) assessing the effect of more intensive BP lowering compared to less intensive BP lowering on patients who underwent endovascular thrombectomy due to ischaemic stroke are included in our meta-analysis.

Exclusion criteria

All study types other than RCTs, and those that did not measure our outcomes were excluded.

Information sources and search strategy

To comprehensively gather relevant studies, we searched critical electronic databases such as the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (*via* PubMed), Embase (*via* Ovid) and ClinicalTrials.gov. Grey literature sources like ProQuest and OpenGrey were also used to find relevant RCTs. Reference lists of included articles and relevant reviews were searched to ensure a comprehensive search. Different keywords like 'ischemic stroke', 'endovascular thrombectomy' and 'blood pressure management' were used to search for relevant RCTs. The detailed search strategy is shown in Supplementary Table 1.

Outcome measures

The primary outcome of interest is the incidence of 90-day mRS scores ranging from 0 to 2. Additionally, secondary outcomes include the incidence of 90-day mortality, any intracerebral haemorrhage (ICH) and severe ICH.

Study selection and data extraction

All the articles retrieved from the search were imported into Mendeley Desktop 1.19.8. After deduplication, two reviewers carried out the screening process. Screening was done, first according to the title and abstract of the studies and then by reading the full text of the articles. Any disagreements during full-text screening were resolved through discussion; in some cases, a third reviewer acted as an arbiter. The study selection process has been represented *via* a PRISMA flowchart (Figure 1).

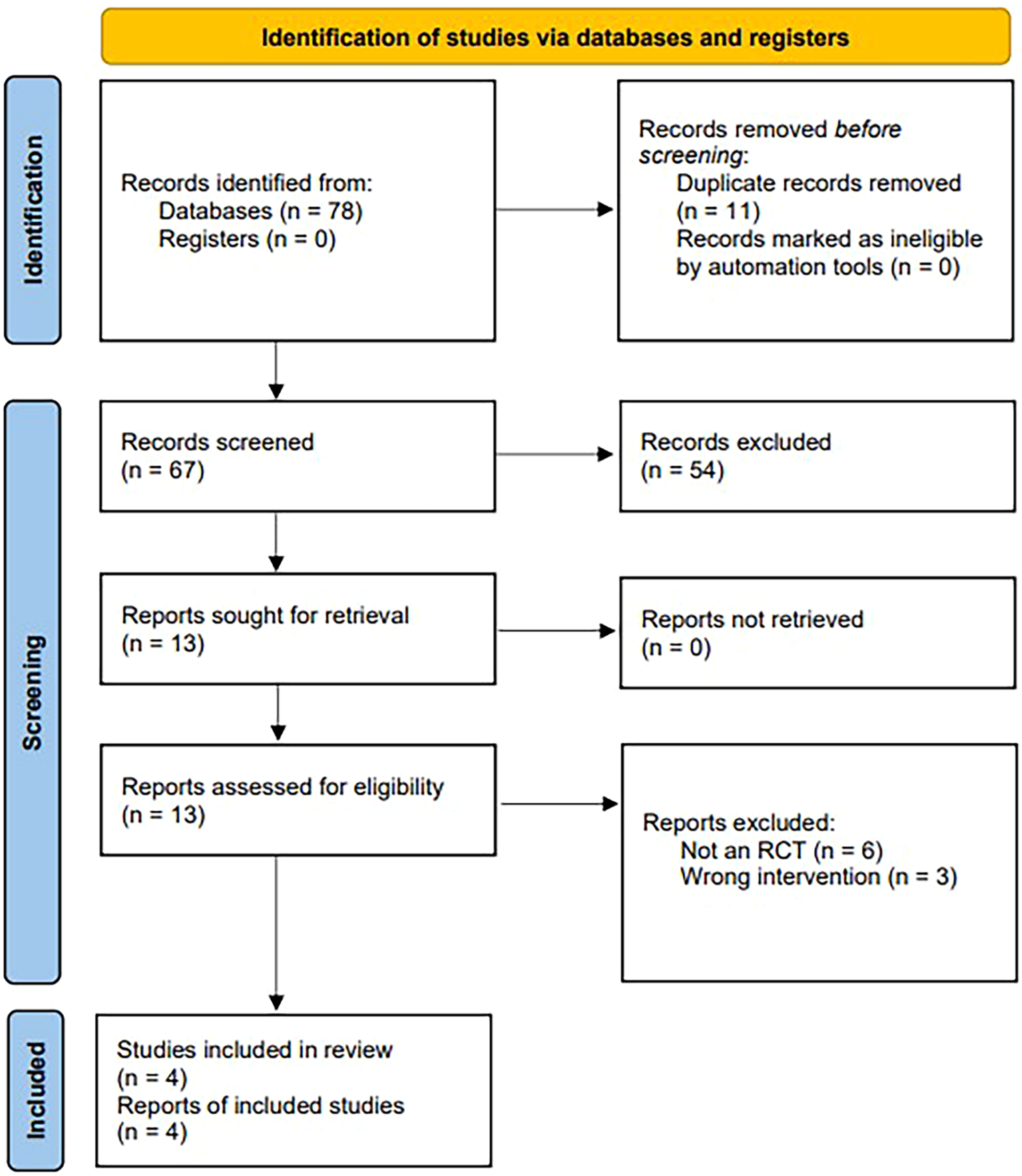

Figure 1. PRISMA 2020 flow chart. Flow chart of included and excluded trials. PRISMA, Preferred Reporting Items for Systematic Reviews and meta-analyses.

After the study selection, two reviewers extracted the subsequent data into a structured Excel spreadsheet using a pre-piloted form. The extracted information included study characteristics, participant details, intervention specifics and outcome measures. A third reviewer resolved any discrepancy.

Risk of bias assessment

The risk of bias in the included studies was assessed using the revised Cochrane 'Risk of bias' tool for randomised trials (RoB 2.0). Two reviewers independently evaluated five specific bias domains, resolving disagreements through discussion or involving a third reviewer if necessary. They graded each included study as low, high or some concerns regarding bias. The risk of bias in all included studies is presented in Supplementary Figure 1.

Data synthesis

We reported dichotomous outcomes as odds ratio (OR) and 95% confidence intervals (CIs). We used the DerSimonian and Laird random-effects model in our meta-analyses. We calculated the Chi^2 test and I^2 statistic to detect and quantify heterogeneity. We interpreted I^2 values according to the Cochrane Handbook for Systematic Reviews of Interventions, section 10.10. Regarding interpreting I^2 values, 0–40% might not be important, 30–60% may represent moderate heterogeneity, 50–90% may signify substantial heterogeneity and 75–100% accounts for considerable heterogeneity. $p < .10$ was considered statistically significant for the Chi^2 test. All statistical analyses were performed using Review Manager (RevMan, Version 5.4; The Cochrane Collection, Copenhagen, Denmark). The study characteristics and findings of the included studies were presented as tables. We conducted a sensitivity analysis of all outcomes based on the fixed effects model. For all outcomes, we constructed a funnel plot and checked funnel plot asymmetry through Egger's test using Comprehensive Meta-Analysis 4 software. Publication bias is considered to be present when the p-value is less than .10.

Results

Study selection and characteristics of included studies

After applying the eligibility criteria, four RCTs comprising 1560 patients [18,19, 22,23] were included in our meta-analysis. The age range of participants in all four studies was 68–82 years. BP targets varied slightly among different studies and are presented in Table 1. The study characteristics of each study are displayed in Table 1. PRISMA figure of study selection process is presented as Figure 1.

The risk of bias was found to be low in all RCTs except two trials. The study by Mazighi et al. [23] had a high risk of bias due to concerns regarding the randomisation process and deviations from intended interventions.

Outcomes

Incidence of 90-day mRS= 0–2 score

In our analysis, we found that more intensive BP management was associated with a statistically significant decrease in patients showing functional independence (mRS score = 0–2) at 90 days (OR 0.69; CI = 0.51-0.94; Figure 2). There was moderate statistical heterogeneity (I^2 = 44%) among different studies. No funnel plot asymmetry was detected (Egger's p-value = .35; Supplementary Figure S2).

Incidence of 90-day mortality

Our pooled results showed no statistically significant difference between the more intensive BP management group and the less intensive BP management group (OR 1.21; CI = 0.89–1.65; Figure 3). The heterogeneity was minimal among different studies (I^2 = 0%). We found no funnel plot asymmetry (Egger's p-value = .43; Supplementary Figure S3).

Incidence of any ICH

There was no statistically significant difference between the two groups for the incidence of ICH (OR 1.09; CI = 0.85–1.39; Figure 4). The heterogeneity was calculated to be 0%. No funnel plot asymmetry was detected (Egger's p-value = .98; Supplementary Figure S4).

Incidence of symptomatic ICH

There was no statistically significant difference between the two groups for the incidence of sICH (OR 1.11; CI = 0.75–1.65; I^2 = 0%; Figure 5). No funnel plot asymmetry was detected (Egger's p-value = .99; Supplementary Figure S5).

Sensitivity analysis

According to our analysis using a fixed effects model, we found similar results for all the outcomes.

Table 1. Characteristics of included studies.

Study ID	Yang 2022	Mazighi 2021	Nam 2023	Mistry 2023
Country	China	France	South Korea	US
Mean age, years	68 ± 4.9 vs 67 ± 4.9	76.25 ± 5.5 vs 74 ± 5.8	73.2 ± 12.1 vs 72.9 ± 10.8	74.9 ± 5.2 vs 69.7 ± 4.0 vs 67.6 ± 5.3
Male, *n* (%)	249 (61%) vs 257 (63%)	81/158 (51%) vs 72/160 (45%)	92(59.4%) vs 88(59.9%)	12(30%) vs 19(47.5%) vs 20(50%)
Sample size	407 + 409 = 816	158 + 160 = 318	155 + 151 = 306	40 + 40 + 40 (120)
Blood pressure targets	SBP: 120 vs 140–180	100–129 vs 130–185	SBP: <140 vs 140–180	<140 vs <160 vs <= 180
Past history of hypertension, *n* (%)	267 (66%) vs 261 (63.8%)	72/160 (45%) vs 113/160 (71%)	121(78.1%) vs 110(74.8%)	32(80%) vs 28(70%) vs 32(80%)
Past History of diabetes, *n* (%)	81 (19.9%) vs 82 (20%)	34/155 (22%) vs 33/159 (21%)	65(41.9%) vs 62(42.2%)	12(30%) vs 15(37.5%) vs 13(32.5%)
Past History of hyperlipidaemia, *n* (%)	14 (3.4%) vs 13 (3.2%)	59/153 (39%) vs 55/158 (35%)	61(39.4%) vs 54(36.7%)	33(82.5%) vs 28(70%) vs 34(85%)
Baseline antiplatelet use, *n* (%)	34 (8%) vs 39 (10%)	44/156 (28%) vs 37/160 (23%)	NA	14(35%) vs 13(32.5%) vs 19(47.5%)
Baseline anticoagulant use, *n* (%)	20 (5%) vs 20 (5%)	36/156 (23%) vs 34/160 (21%)	NA	10(25%) vs 3(7.5%) vs 9(22.5%)
Mean NIHSS score	15 vs 15	18 (12–20) vs 17 (13–20)	NIHSS score: 0–5:14 vs 18 6-15: 83 vs 89 >/=16: 58 vs 50	
mTICI score 2b, *n* (%)	37 (9%) vs 43 (11%)	70/158 (44%) vs 76/160 (48%)	NA	16 (40%) vs 17 (42.5%) vs 17 (42.5%)
mTICI score 2c, *n* (%)	28 (7%) vs 26 (6%)	NA	NA	6 (15%) vs 5 (12.5%) vs 7 (17.5%)
mTICI score 3, *n* (%)	342 (84%) vs 340 (83%)	88/158 (56%) vs 84/160 (52%)	NA	18 (45%) vs 18 (45%) vs 16 (40%)
Occlusion site Isolated Middle Cerebral Artery (MCA)	NA	117/158 (74%) vs 119/158 (75%)	NA	M1= first segment of MCA; M2 = second segment of MCA M1 31 (77.5%) vs 25 (62.5%) vs 23 (57.5%) M2 6 (15%) vs 8 (20%) vs 15 (37.5%)
Occlusion site Tandem MCA or Internal Carotid Artery (ICA)	M1 segment of the middle cerebral artery (310 [48%] of 643 patients)	41/158 (26%) vs 39/158 (25%)	NA	ICA: 7 (17.5%) vs 9 (22.5%) vs 5 (12.5%)
Functional independence at 3 months (mRS score: 0–2), No./total (%)	192/404 (48%) vs 247/406(61%)	67/152 (44%) vs 69/153 (45%)	61/155(39.9%) vs 80/147 (54.4%)	17/37(45.9%) vs 17/39(43.5%)
Incidence of any ICH ≤36 h	112/407 vs 102/409	65/154 vs 68/157	12/155 vs 12/149	26/76 vs 12/40
Incidence of symptomatic ICH ≤36 h	23/407 vs 25/409	17/154 vs11/157	14/155 vs 12/149	3/72 vs 2/37
All-cause mortality	66/406 vs 61/408	32/152 vs 24/153	–	9/80 vs 3/40

Study or Subgroup	More Intensive Events	More Intensive Total	Less Intensive Events	Less Intensive Total	Weight	Odds Ratio IV, Random, 95% CI
Mazighi 2021	67	152	69	153	25.7%	0.96 [0.61, 1.51]
Mistry 2023	17	37	17	39	9.5%	1.10 [0.45, 2.72]
Nam 2023	61	155	80	147	25.3%	0.54 [0.34, 0.86]
Yang 2022	192	404	247	406	39.5%	0.58 [0.44, 0.77]
Total (95% CI)		**748**		**745**	**100.0%**	**0.69 [0.51, 0.94]**
Total events	337		413			

Heterogeneity: Tau² = 0.04; Chi² = 5.31, df = 3 (P = 0.15); I² = 44%
Test for overall effect: Z = 2.38 (P = 0.02)

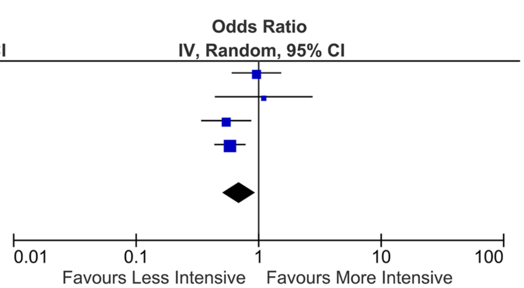

Figure 2. Comparison of participants showing functional independence (modified rankin scale [mRS score] = 0–2) at 90 days between more intensive blood pressure control and less intensive blood pressure control.

Discussion

In our meta-analysis of four RCTs with 1560 patients, we assessed the safety and efficacy of intensive BP management compared to conventional BP management in patients who underwent endovascular thrombectomy for AIS. Our analysis showed that intensive BP lowering is associated with a significant decline in functional independence (mRS score = 0–2) compared to the conventional BP lowering. There was no statistically significant difference between the intensive BP lowering treatment group and the conventional BP management group regarding 90-day mortality [18,19, 22,23]. Furthermore, lowering intensive BP had no significant effect on the incidence of

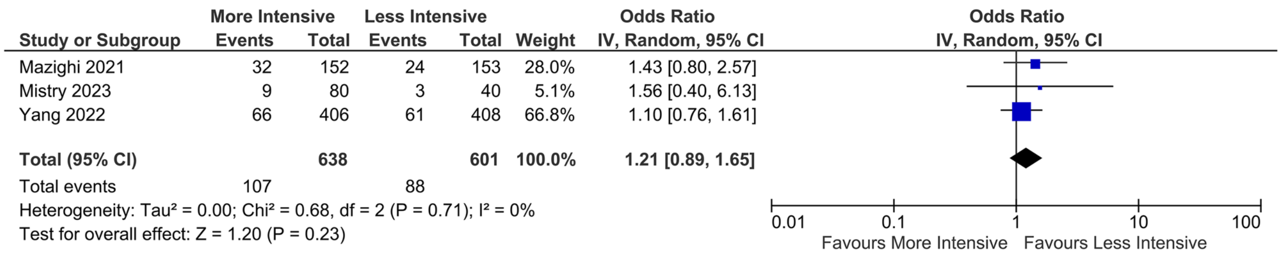

Figure 3. Comparison of 90-day mortality between more intensive blood pressure control and less intensive blood pressure control.

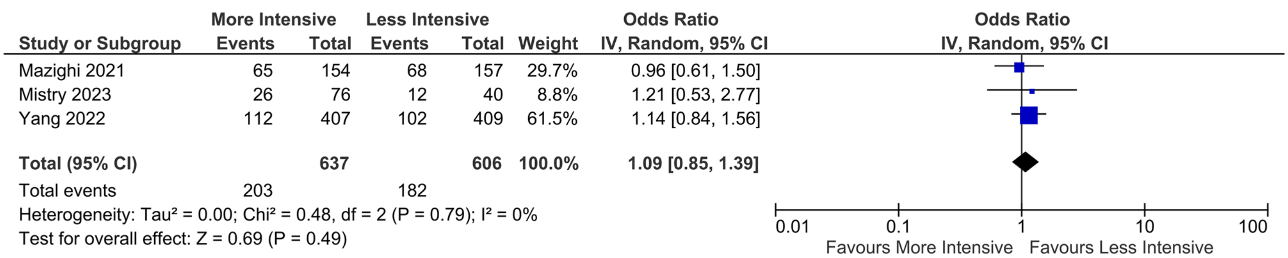

Figure 4. Comparison of incidence of intracerebral haemorrhage (ICH) between more intensive blood pressure control and less intensive blood pressure control.

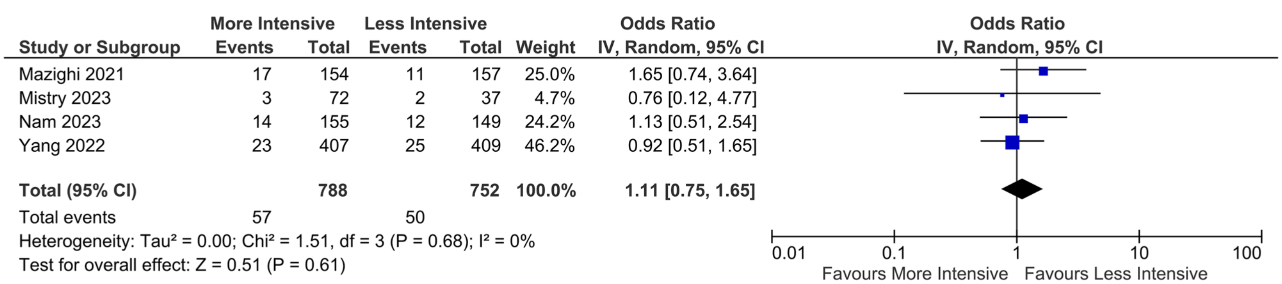

Figure 5. Comparison of incidence of severe intracerebral haemorrhage (sICH) between more intensive blood pressure control and less intensive blood pressure control.

ICH and was equivalent to conventional management [18,19, 22,23].

According to the previous meta-analysis by Zhou et al. [17], the intensive BP lowering was favourable than conventional BP lowering after successful endovascular thrombectomy for AISs. Their analysis included only two RCTs and mixing of data from RCTs and observational studies. According to their results, the proportion of patients showing functional independence at 90 days was significantly lower in the intensive BP lowering group (SBP < 130 mmHg) compared to the conservative group (SBP < 140 mmHg) [17]. Zhou et al. [17] reported no statistically significant difference in 90-day mortality between the two BP-lowering groups. These results agree with our pooled analysis. Regarding the incidence of ICH, they reported that intensive BP lowering (SBP < 140 mmHg) was associated with better outcomes, that is there was a statistically significant decrease in the incidence of symptomatic ICH compared to conventional management [17]. However, our analysis showed no statistically significant difference in the incidence of sICH between intensive BP lowering and worse functional outcomes. These dissimilar findings could be explained by the overall lower risk of bias in our study, as we included only RCTs in our analysis. It could also be explained by the inclusion of the two large-scale RCTs in our study.

The review encompasses research completed across diverse resource settings and ethnic communities, augmenting our findings' generalisability. Our study reduced bias by including only RCTs and increased overall power by combining the results of four RCTs, which involved 1560 patients.

It is imperative to consider the limitations of our analysis. Despite pooling a large cumulative sample size, our meta-analysis was still underpowered for most clinical outcomes assessed, as indicated in the results. The included RCTs had varying and overlapping BP ranges for intensive and less intensive treatment. Another limitation of the study was that we evaluated study-level data instead of patient-level data, which is a better data source.

Regarding the flaws associated with the RCTs in this study, all four used robust randomisation processes. Three of them implemented blinded-endpoint designs to reduce the bias inherent in the open-label format, which was necessary because the nature of the intervention could not be concealed from participants and clinicians. However, for one RCT [23], there are some concerns regarding the blinding process.

According to our analysis, we suggest conservative BP management following a successful EVT as functional independence is achieved at lower rates after intensive BP lowering. Although there is an overlap between SBP parameters for the intensive group, the conventional group in all RCTs consisted of those with SBP <180mm Hg. Till we have more data to reliably say otherwise, we should not lower BP unless SBP goes above 180 after thrombectomy.

Further studies in the future should be aimed at identifying individual BP-lowering drugs and their effects on mortality. Future RCTs should also be conducted to determine the impact of other interventions, such as early initiation of dual antiplatelet and lipid-lowering agents, in lowering post-stroke mortality following thrombectomy.

Conclusion

According to our meta-analysis, the intensive BP lowering group was associated with a lower number of patients showing functional independence at 90 days. We found no benefit of the intensive lowering of BP on mortality rates and incidence of ICH compared to the conservative BP management. Our strength of evidence is low to moderate because of the small sample size and bias present in the included studies. Future large-scale trials should focus on other interventions to improve prognosis in these patients.

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Consent

No consent was required for this study.

Disclosure statement

The authors declare that they have no conflicts of interest and no financial interests related to the material of this manuscript.

Ethics approval

No ethical approval was required for this study.

Funding

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