Journal of Stroke and Cerebrovascular Diseases 33 (2024) 107641

Contents lists available at ScienceDirect

Journal of Stroke and Cerebrovascular Diseases

journal homepage: www.elsevier.com/locate/jstroke

Intravenous thrombolysis for ischemic stroke in the posterior circulation: A systematic review and meta-analysis

Robrecht R.M.M. Knapen, M.D. [a,*,1], Senta Frol, M.D., Ph.D. [b,1], Sander M.J. van Kuijk, Ph.D. [c], Janja Pretnar Oblak, M.D., Ph.D [b], Christiaan van der Leij, M.D., Ph.D. [d], Robert J. van Oostenbrugge, M.D., Ph.D. [e], Wim H van Zwam, M.D., Ph.D. [a]

[a] Department of Radiology and Nuclear Medicine, Maastricht University Medical Center+ and CARIM, School for Cardiovascular Diseases, Maastricht University, Maastricht, the Netherlands
[b] Departmenta of Vascular Neurology, University Medical Center Ljubljana and Faculty of medicine, University of Ljubljana, Ljubljana, Slovenia
[c] Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center+, Maastricht, the Netherlands
[d] Department of Radiology and Nuclear Medicine, Maastricht University Medical Center+, Maastricht, the Netherlands
[e] Department of Neurology, Maastricht University Medical Center+ and CARIM, School for Cardiovascular Diseases, Maastricht University, Maastricht, the Netherlands

ARTICLE INFO

Keywords:
Acute ischemic stroke
Posterior circulation
Meta-analysis
Basilar artery occlusion (BAO)
Intravenous thrombolysis (IVT)
Posterior circulation strokes (PCS)

ABSTRACT

Objectives: Intravenous thrombolysis (IVT) is recommended in patients with ischemic stroke in the anterior and posterior circulation. Neurological outcomes due to posterior circulation strokes (PCS) without treatment remain poor. Our aim was to overview the literature on outcomes of IVT and conservative treatment in PCS, based on a systematic review and meta-analysis.

Methods: A systematic literature search was performed on February 27th 2023. Outcome measures included favorable functional outcome at 90 days (modified Rankin Scale [mRS] 0-2), mortality at 90 days, and symptomatic intracranial hemorrhages (sICH). Weighted averages with DerSimonian-Laird approach was used to analyze the data. Subgroup analyses by time window were performed: standard time window (<4.5 hours after symptom onset) and extended time window (>4.5 hours). Analyses were performed using R.

Results: Eight prospective and four retrospective cohort studies were included (n = 1589 patients); no studies with conservative treatment were eligible. The pooled weighted probability regarding favorable functional outcome after IVT was 63 % (95 %CI:0.45-0.78), for mortality 19 % (95 %CI:0.11-0.30), and for sICH 4 % (95 % CI:0.02-0.07). Subgroup analyses showed higher probabilities on achieving favorable functional outcomes for patients treated in the standard (77 %; 95 %CI:0.62-0.88) compared to the extended time window (38 %; 95 % CI:0.29-0.48) with RR = 1.93 (95 %CI:1.66-2.24). Lower probabilities regarding mortality at 90 days and sICH were seen in patients treated in standard compared to extended time window (RR = 0.42, 95 %CI:0.34-0.51 and RR = 0.27, 95 %CI:0.16-0.45, respectively).

Conclusions: IVT in patients with PCS seems to be safe and effective in standard and extended time window. The effect of IVT is higher in the standard time window.

Introduction

Ischemic strokes in the posterior circulation occur approximately in 20 % of all stroke cases.[1] Posterior circulation strokes (PCS) include occlusions in the vertebral, basilar, posterior cerebral artery (PCA), and their side branches.[2,3] Mortality rates vary from 7 % up to 90 %, depending on the location of the occlusion.[4–7] Acute basilar artery occlusions (BAOs) represent 5–10 % of all strokes and carry a very high mortality rate, up to 90 % if untreated.[1,4,5]

Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA, alteplase) is safe and effective in patients with an acute ischemic stroke (AIS) in the anterior circulation. IVT is recommended within 4.5 hours after start of stroke symptoms,[8] but it has been shown that selected patients with unknown stroke onset time or if stroke

* Corresponding author at: Maastricht University Medical Center+, Department of Radiology and Nuclear medicine, P. Debyelaan 25, 6229HX, Maastricht, the Netherlands.
E-mail address: robrecht.knapen@mumc.nl (R.R.M.M. Knapen).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107641
Received 8 December 2023; Received in revised form 6 February 2024; Accepted 18 February 2024
Available online 21 February 2024

symptoms started beyond 4.5 hours may also benefit from IVT.[9,10] Endovascular treatment (EVT) is the therapy of choice in AIS patients with large vessel occlusions (LVO).[11] Additional value of IVT prior to EVT in patients with LVO was extensively debated over the last years leading to reassuring results of non-omitting IVT prior EVT unless there are contraindications for IVT.[12,13]

Although EVT has been proven to be effective and safe in BAO patients by the ATTENTION and BAOCHE Trial, the BASICS trial failed to prove the effectiveness of EVT in BAO patients.[14–16] A potential explanation was the high administration rate of IVT in the control arm compared to the ATTENTION and BAOCHE Trial. This raised the question about the effect of IVT only in PCS.

To provide a better overview of literature and outcomes, we performed a systematic review and meta-analysis of IVT and conservative treatment in PCS patients. We aimed to perform a direct comparison between both groups, however, this was not possible because of the incomplete data.

Methodology

This systematic review and meta-analysis is conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[17] Data are available on reasonable request.

Search & selection strategy

A literature search was performed in two electronic databases (MEDLINE [through PubMed] and Embase) on published data up to 27 February 2023 (by RRMMK). The search query included the following terms: "Basilar artery", "Posterior circulation", "Stroke", "Brain ischemia", "Intravenous thrombolysis", "Tissue Plasminogen Activator", "Treatment outcome", "Modified Rankin Scale", "Randomized Controlled Trial", and "Cohort studies", which were combined using Boolean operators. The search strategy for each database is provided in the Supplemental Material (Supplemental appendix 1,2). After removing duplicates (in Endnote X9, Thompson Reuters, Philadelphia), all titles and abstract were screened for eligibility (Fig. 1).

Eligibility criteria

All titles and abstracts were screened independently by two authors (RRMMK and SF) for full-text evaluation. Studies were eligible if the following inclusion criteria were met: randomized controlled trials (RCTs) or cohort studies involving humans; patients with PCS; patients treated with IVT, without EVT. When no consensus was reached, a third author decided on eligibility (WHvZ). When studies used different clinical outcome measures or data were not provided in a way comparison was possible, studies were excluded from this systematic review. Since this systematic review and meta-analysis focused on the use of IVT, studies were excluded when no clear distinction was made between patients treated with IVT only and with IVT plus EVT.

Data extraction

Data were extracted and combined in one uniform data sheet by two authors (RRMMK and SF). When studies used data from the same registry, data from the largest study were extracted. The extracted data

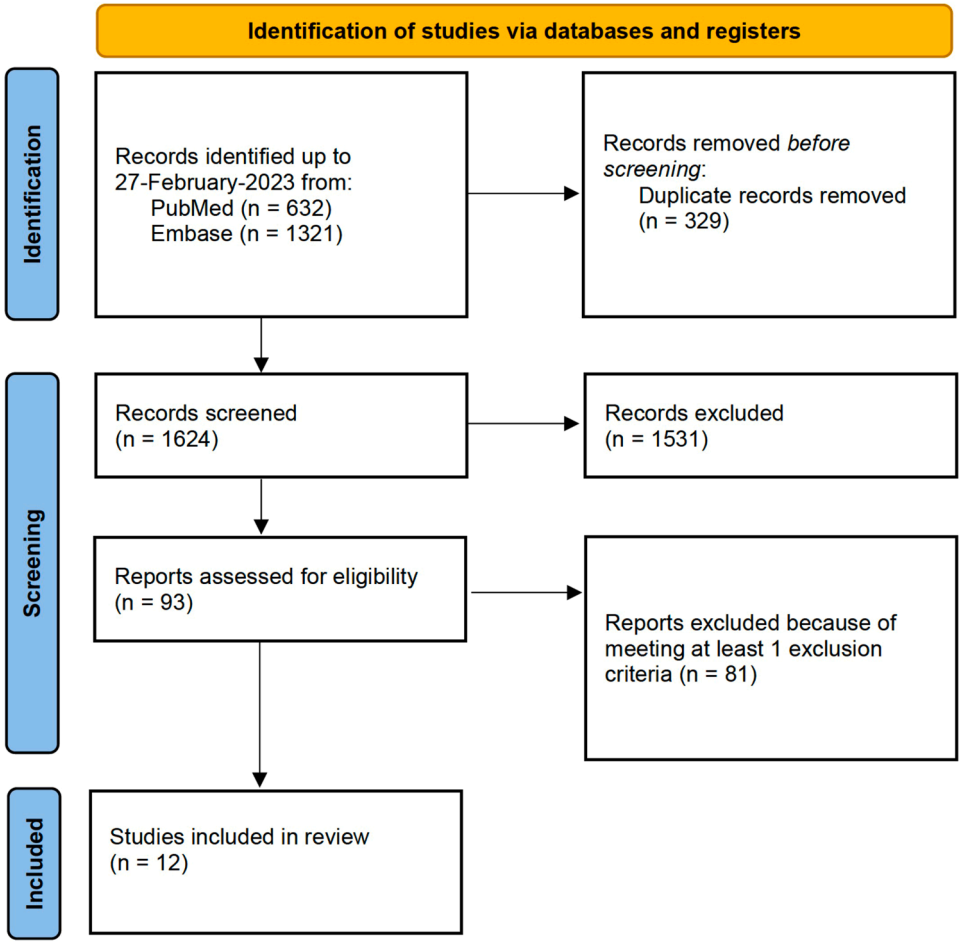

Fig. 1. Flowchart of included studies.

contained the following variables from each study: first author, year, study type, ethnicity, years of inclusions, age, sex, arterial hypertension, atrial fibrillation, National Institutes of Health Stroke Scale (NIHSS) at admission, time between stroke onset and needle placement, mortality at 90 days, modified Rankin Scores (mRS) at 90 days, symptomatic intracranial hemorrhage (sICH) rates, and recanalization rates.

Outcome measurements

The following outcome measurements were considered: good functional outcome (defined as mRS score 0-2) and favorable functional outcome (defined as mRS score 0-3) at 90 days, mortality at 90 days, sICH rates, and successful recanalization rates (see Table S1 for the definitions of successful recanalization).

Risk of bias assessment

Two authors (RRMMK and SF) assessed the included studies independently for Risk of Bias, using the Newcastle-Ottawa Scale for cohort studies.[18] When no consensus was reached, a third independent author was asked (WHvZ). All studies were scored on 8 items, divided into three domains:[1] Selection,[2] Comparability, and[3] Outcome. One point for every item, except for the comparability item, which can be given 2 points (Table S2).

Data analysis

Study characteristics are described using descriptive statistics. An assessment was made to identify if a meta-analysis could be performed. When necessary, data were transformed from median to mean and from interquartile range [IQR] to standard deviation (SD), using the method described by Cochrane.[19] To calculate the mean with SD, we assumed normally distributed data, therefore median was equal to mean. The IQR was transformed into SD by dividing the IQR by 1.35, as about 50 % of all observations in a normal distributed variable fall between the mean minus and plus 1 SD. If necessary, multiple means and standard deviations within studies were pooled.

A random-effects model with DerSimonian-Laird approach was used to pool results from the included studies as we anticipated substantial heterogeneity between the studies and the patient populations they recruited. Heterogeneity was quantified as Higgin's I^2 statistic; a I^2 value of 50–75 % was considered as moderate heterogeneity and more than 75 % as high heterogeneity. Results from the random-effect models are presented including their 95 % confidence interval (CI) and visualized using forest plots. All analyses were performed using R (Version 4.1.2) and the alpha was set at 5 %.

Subgroup analysis

We performed a subgroup analysis by treatment time window (standard versus extended time window) on study-level. Standard window was defined as patients treated within 4.5 hours after symptoms onset, and extended time window as treated after 4.5 hours with a maximum up to 48 hours. When IVT was recommended within 4.5 hours, but the mean duration was more than 4.5 hours, the study was placed in the extended time window. To calculate the risk ratios (RR) between the groups, we pooled the raw data of the studies and used the inverse variance method. Secondly, a sensitivity analysis was performed in which the same outcome measures were analysed in patients with only a BAO. Similar forest plots were made as for our main analyses.

Results

A total of 1933 articles were extracted. After removal of the duplicates, 1624 studies were screened. A total of 93 articles were selected for full-text review, twelve articles met the inclusion criteria and were included (Fig. 1).[20–31] Table S1 shows the study characteristics and patient's characteristics. Four studies collected data retrospectively[21,26–28] and eight prospectively.[20,22–25,29–31] The risk of bias assessment of the twelve included cohort studies is reported in Table S2 with eight studies revealing high quality.[20–22,24,27–30] Six cohort studies or case-series of conservatively treated patients were excluded because different clinical outcome measures were used, and data were not suitable for analysis, making direct comparisons between patients treated with IVT and without IVT impossible.[32–37]

A total of 1658 patients were included in the meta-analysis. The mean age was 67.3 years, and 602 (37.9 %) patients were female. In seven studies (n = 1286) patients were treated within 4.5 hours after symptoms onset.[22,23,25,26,28,29,31] The overall pooled mean time from stroke onset to treatment was 220.2 minutes (95 %CI:167.9-288.7) (Fig. 2).

Good functional outcome (mRS 0-2) at 90 days

Nine studies (n = 1264 patients) reported good functional outcome rates (mRS 0-2) at 90 days.[20,22–24,26–30] The overall pooled probability of good functional outcome after treatment with IVT was 63 % (95 % CI:0.45-0.78) (Fig. 3A), but heterogeneity between the pooled studies was high (I^2 = 94 %). Standard time window was favoured over extended time window regarding good functional outcome (RR = 1.93; 95 %CI: 1.66-2.24), showing a higher pooled proportion of 77 % (95 % CI:0.62-0.88; I^2 = 89 %) compared to the extended time window treated patients (38 %; 95 %CI:0.29-0.48; I^2 = 63 %).

Favorable functional outcome (mRS 0-3) at 90 days

Only two studies,[21,24] both extended time window studies, reported favorable outcome (mRS 0-3) at 90 days as outcome measure. A total of 222 patients were included, 88 patients had a mRS of 0-3 after 90 days follow-up (Fig. 3B). The overall pooled proportion was 34 % (95 % CI:0.17-0.56; I^2 = 58 %).

Mortality at 90 days

The mortality at 90 days was presented in ten studies (n = 1293 patients) (Fig. 3C).[20–24,26,27,29–31] A total of 269 patients (19 %) died within 3 months. Standard time window treatment resulted in lower mortality rates compared to extended time window treatment (RR = 0.42; 95 %CI:0.34-0.51) with a pooled probability of 12 % (95 % CI:0.08-0.19; I^2 = 74 %) compared to 36 % (95 %CI:0.30-0.43; I^2 = 55 %), respectively.

Symptomatic intracranial hemorrhage

Eleven studies (n = 1527 patients) presented the sICH rates,[20–22,24–31] with an overall pooled proportion of 4 % (95 %CI:0.02-0.07; I^2 = 73 %) (Fig. 4A). The random effects model showed lower proportions of sICH in standard time window treated patients (3 %, 95 % CI:0.02-0.04; I^2 = 10 %) compared to extended time window patients (7 %, 95 %CI:0.04-0.13; I^2 = 28 %), resulting in lower risk ratio for patients treated in standard time window (RR = 0.27; 95 %CI:0.16-0.45).

Successful recanalization

Three extended time window studies and one standard time window study (n = 335 patients) reported successful recanalization rates.[20,21,24,28] Analysis showed a pooled proportion of successful recanalization of 62 % (95 %CI:0.55-0.75) in the standard time window and 61 % (95 %CI:0.55-0.67) in the extended time window (Fig. 4B). The risk ratio for higher successful recanalization rates for patients treated in the standard time window compared to the extended time window was RR = 1.07 (95 %CI:0.89-1.27).

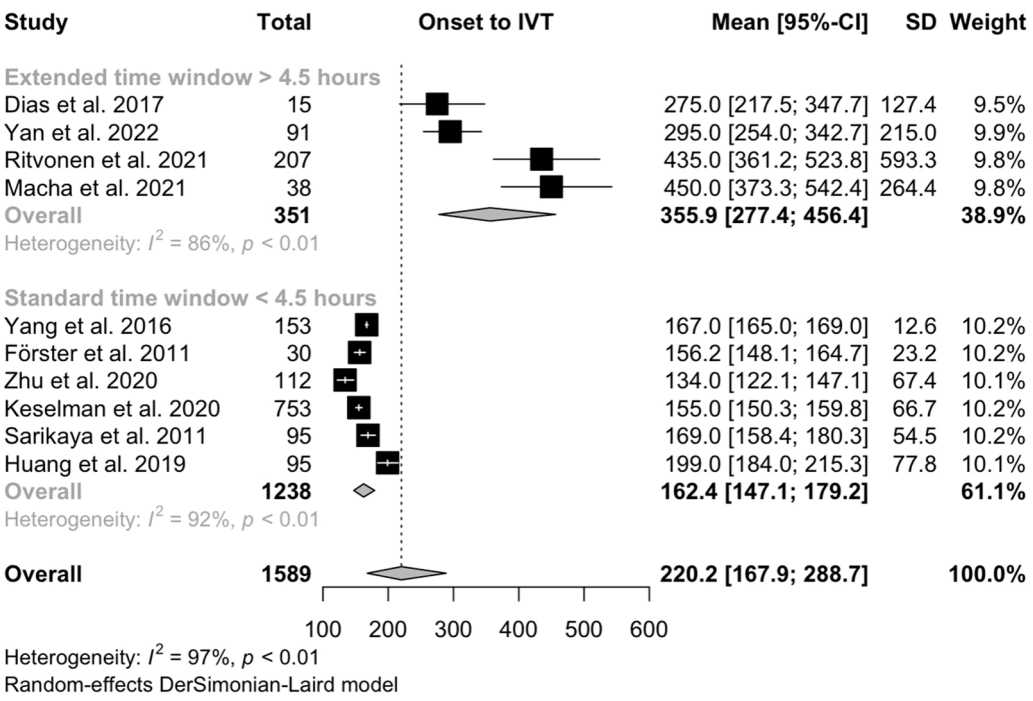

Fig. 2. Forest plots of pooled average onset to intravenous thrombolysis time.

BAOs

In total three studies (n = 313 patients) included only BAOs.[20,21,24] All three studies were extended time window studies with a pooled average onset to IVT time of 328.9 minutes (95 %CI:249.1-434.3; $I^2 = 85$ %) (Fig. 5A). The favorable functional outcome at 90 days pooled proportion was 34 % (95 %CI:0.17-0.56; $I^2 = 58$ %) (Fig. 5C), for mortality at 90 days it was 39 % (95 %CI:0.33-0.44; $I^2 = 0$ %) (Fig. 5D), and for sICH 9 % (95 %CI:0.05-0.15) (Fig. 5E).

Discussion

We conducted a systematic review and meta-analysis of IVT in PCS patients to overview the efficacy and safety of IVT, since no direct comparison was possible with conservative treated PCS patients. Additionally, a subgroup analysis comparing standard versus extended time window was performed, as well as a sensitivity analysis with only BAO studies. Treatment in the standard time window resulted in higher rates of good and favorable functional outcome compared to the extended time window. Mortality at 90 days and sICH rates were also more favorable for patients treated with IVT in the standard window compared to extended time window. Since all three BAO-only studies were in the extended time window, the results of the BAO sensitivity analyses were comparable to the extended time window in PCS of our main analyses.

Natural history of PCA and side branches occlusion strokes are assumed to be less severe compared to BAOs strokes, with mortality rates up to 11 % and 7 % respectively, when treated conservatively.[6,7] One large cohort (n = 282) study showed independency at 3 months in 69 % of the patients with side branches occlusion strokes, and one study showed a mRS <2 at 6 months in 56 % of the PCA stroke patients.[7,38] Since our mRS 0-2 rate is 63 %, which is comparable, one may assume that the treatment effect if IVT is of limited added value when there is only an occlusion in the side branches or in the PCA.

BAOs present with different clinical symptoms and result in higher mortality and morbidity rates.[39–41] Most literature show mortality and morbidity rates of over 70 %.[1,4,42–44] When no recanalization is reached in BAO patients, they have approximately 2 % probability of achieving good functional outcome (mRS 0-2).[42,45] Literature on conservative treatment in patients with BAO is scarce and inconsistent. Schonewille et al. reported a mortality rate of 40 %, and favorable functional outcome of 21 % (mRS 0-3) in 82 conservatively treated patients with BAO.[32] Two observational studies showed higher rates of minor deficit in BAO patients treated conservatively (71 % (n = 87) and 71 % (n = 61), respectively), but in a highly selected group of patients, with and without complete occlusions, and with different definitions of clinical outcome.[33,34] Another study (included in this meta-analysis), compared IVT only, EVT only, and conservatively treated BAO patients.[21] Mortality in conservatively treated patients was 84 % and a mRS of 0-3 was achieved in only 7 %. However, it needs to be mentioned that a selection bias cannot be ruled out, as all patients were treated in the extended time window and showed more ischemia at baseline (posterior circulation Alberta Stroke Programme Early CT Score (pc-ASPECTS) <8). The BAO subgroup analysis in our meta-analysis showed a lower mortality rate of 39 %, and a higher mRS 0-3 rate (34 %) compared to above mentioned literature, suggesting efficacy of IVT treatment only in BAO, but power was lacking to draw solid conclusions.

When comparing outcomes of best medical management (BMM) (which includes IVT when indicated) and EVT combined with IVT, the ATTENTION and BAOCHE trials concluded efficacy of EVT plus BMM in BAO patients compared to BMM only.[14,15] The BASICS trial could not show this efficacy of EVT in BAO patients.[16] In the BASICS trial, IVT was administered in nearly 80 % of patients in the BMM group, while this rate was only 30 % and 17 % in the ATTENTION and BAOCHE trials. This may suggest that the high mRS 0-3 rate in the BASICS (38 %), when compared to the ATTENTION (23 %) and BAOCHE (24 %), could have been the effect of IVT, at least partially. Additionally, a recent systematic review observed lower mortality probabilities in BAO patients treated with EVT compared to IVT (31.4 % versus 43.2 %, P = .008), but comparable good functional outcomes (mRS 0-2: 35.2 % versus 31.6 %, P = .36).[46] The high rate of mortality in the IVT group (43.2 %), is comparable to the mortality rate of 38 % observed in our meta-analysis, underlining the severity of BAO occlusions. The same applies to the good functional outcome, with 31.6 % of the patients achieving a mRS 0-2 after IVT in the review, compared to 35 % in our sensitivity analysis. However, the systematic review does not differentiate on time windows.

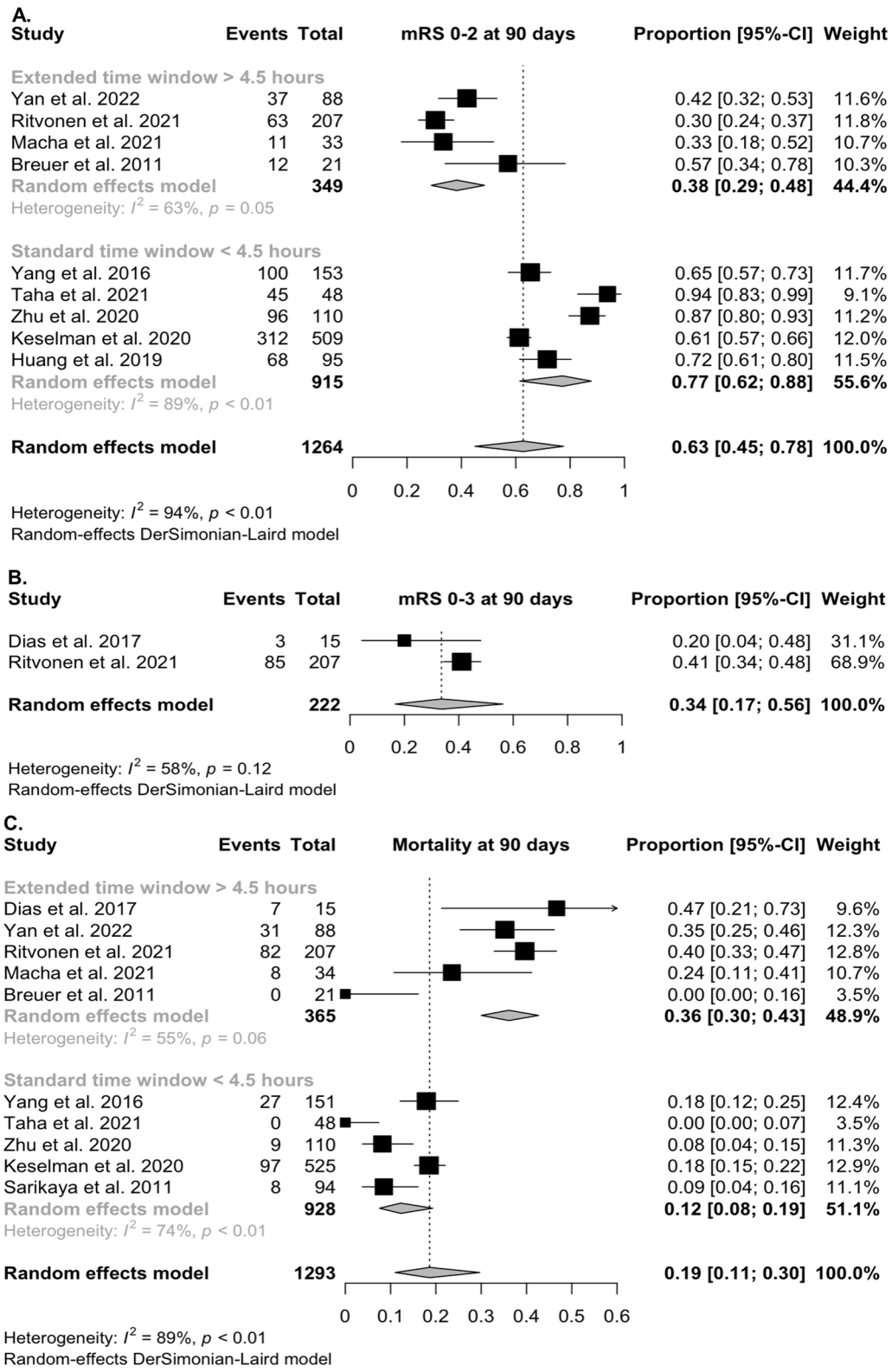

Fig. 3. Forest plots of pooled proportions of clinical outcomes. **A.** Modified Rankin Scale 0-2 at 90 days. **B.** Modified Rankin Scale 0-3 at 90 days. **C.** Mortality at 90 days.

The comparable results in IVT treated patients may suggest a benefit of giving IVT in BAO patients compared to conservatively treated patients. The question remains whether IVT prior to EVT is of any added value or can be omitted, depending on the time window.

Our review and meta-analysis has several limitations. First, the inclusion of prospective and retrospective cohort studies with high heterogeneity, and without RCT's may have led to selection bias. Until now, no RCT's are performed on the effectiveness of IVT as treatment alone in the posterior circulation, and future trials are not to be expected due to loss of equipoise by most physicians. Additionally, a patient level

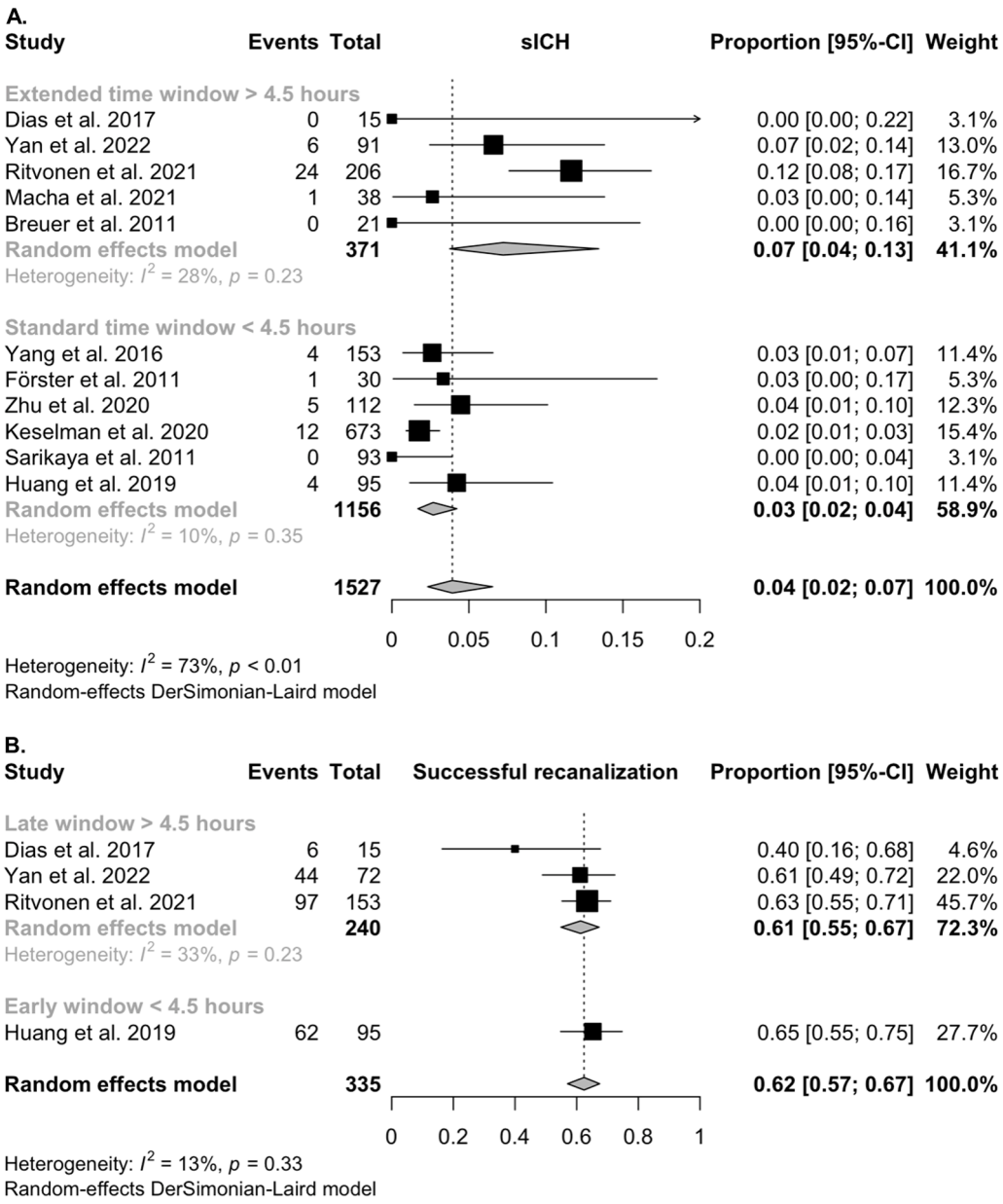

Fig. 4. Forest plots of pooled proportions. **A.** Symptomatic intracranial hemorrhages. **B.** Successful recanalization.

meta-analysis may reduce the heterogeneity, since a distinction would be possibly based on the occlusion location. Unfortunately, the data were not suitable for such analysis. Second, the lack of a comparator group of patients treated without IVT precludes direct comparison with patients with IVT treatment. Our literature search found some cohort studies or case-series of patients with posterior large vessel occlusions treated without IVT and EVT.[32–36] Unfortunately, these studies used different clinical outcome measures and data were not provided in same outcome measurements, making these data unsuitable for comparison. Third, it is known that patients with extensive ischemia (defined as pc-ASPECTS <8) at baseline have higher chances of poor outcome compared to patients with pc-ASPECTS ≥ 8.[47] In our meta-analysis, the pc-ASPECTS score was extracted, but not well enough described and available to include in our analysis, therefore a potential selection bias cannot be ruled out. Fourth, we could not extract data based on the location of the BAOs, since this data was not available. The location of the BAOs and clot length are main predictors of revascularization outcomes.[20,48] Fifth, the heterogeneity in successful recanalization definition and in assessing the rate of successful recanalization among the studies. Different methods, including computed tomography angiography, magnetic resonance angiography, digital subtraction angiography, and transcranial color-coded duplex ultrasonography, were used to determine the modified treatment in cerebral ischemia, the thrombolysis in brain ischemia, or the thrombolysis in myocardial infarction score.

Since our results suggest a benefit of IVT in PCS, especially in the standard time window, the question arises whether this potential benefit is still present when combined with EVT, especially in BAO patients. A future RCT may be needed to investigate the benefit of IVT prior to EVT. Some ongoing RCT's, like the ESCAPE-MeVO (NCT05151172) and DISTAL (NCT05029414), may provide data regarding IVT without EVT in PCA strokes. Although, this may give more insights on the effect of IVT in PCA, the numbers will be limited.

Conclusion

IVT in patients with PCS is safe and effective in standard and extended time window. The effect of IVT is higher in the standard time

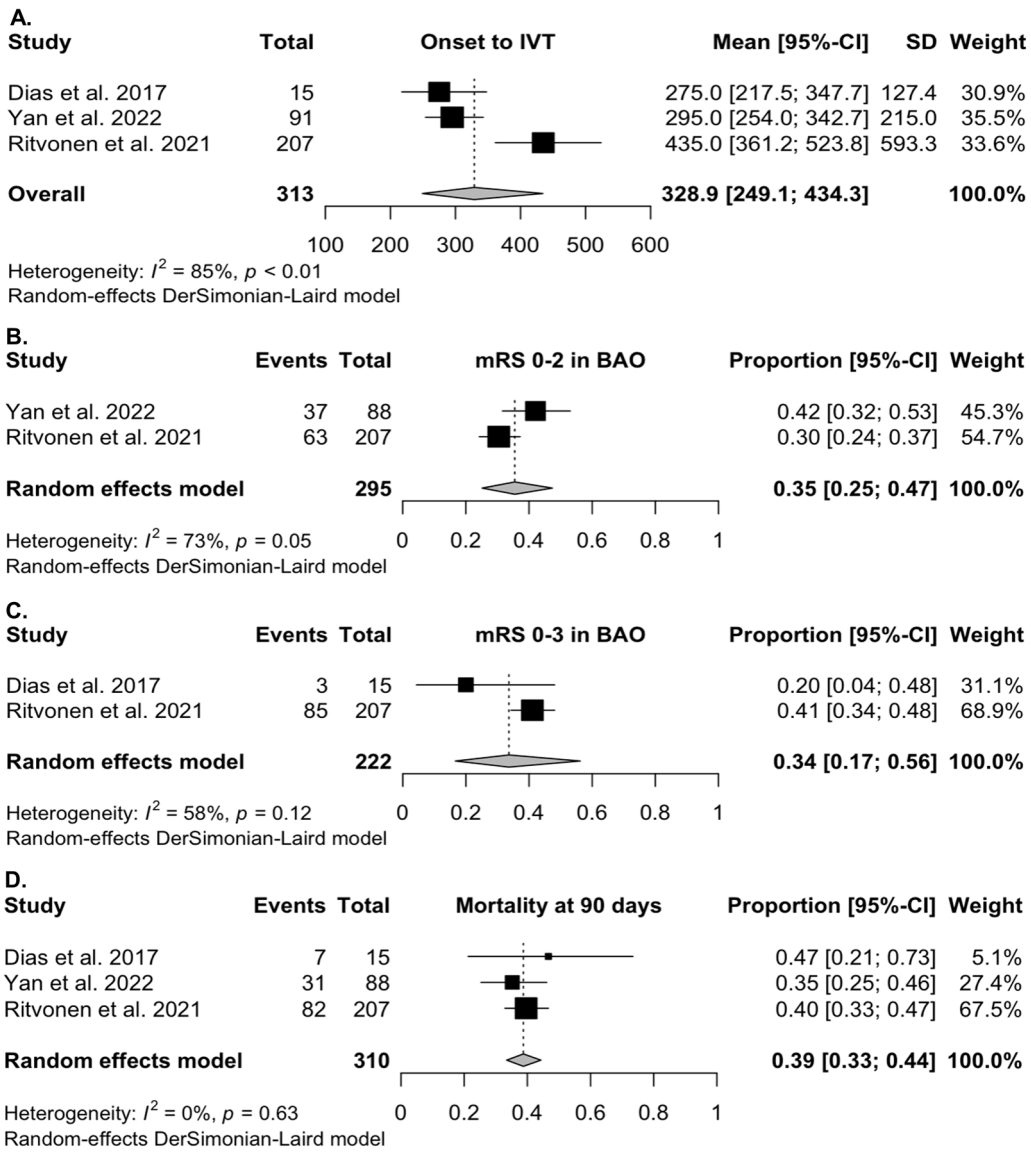

Fig. 5. Forest plots of pooled proportion of studies with only basilar artery occlusions included. **A.** Onset to intravenous thrombolysis time. **B.** Modified Rankin Scale 0-2 at 90 days. **C.** Modified Rankin Scale 0-3 at 90 days. **D.** Mortality at 90 days. **E.** Symptomatic intracranial hemorrhages.

window.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

Not applicable.

Informed consent

Not applicable.

Guarantor

R.R.M.M.K. & W.H.v.Z.

CRediT authorship contribution statement

Robrecht R.M.M. Knapen: Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Senta Frol:** Writing – original draft, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Sander M.J. van Kuijk:** Validation, Methodology, Formal analysis, Data curation, Conceptualization, Writing – review & editing. **Janja Pretnar Oblak:** Writing – review & editing, Supervision, Conceptualization. **Christiaan van der Leij:** Writing – review & editing, Conceptualization, Supervision. **Robert J. van Oostenbrugge:** Writing – review & editing, Supervision. **Wim H van Zwam:** Writing – review & editing, Supervision, Conceptualization, Methodology.

Declaration of competing interest

S.F. & J.P.O.: received speakeŕs honoraria and travel support from Boehringer Ingelheim. W.H.v.Z.: reports speaker fees from Stryker, Cerenovus, and Nicolab, and consulting fees from Philips (all paid to institution); chaired the data safety monitoring boards of WeTrust (Philips), ANAIS (Anaconda) (paid to institution), InExtremis (CHU

Montpellier, Montpellier, France), and DISTAL (Basel, Suisse) (no payments).

Acknowledgements

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2024.107641.

References

1. Schonewille WJ, Wijman CAC, Michel P, Rueckert C, Weimar C, Mattle H, Engelter ST, Tanne D, Muir K, Molina C, et al. Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study. *Lancet Neurol*. 2009;8:724–730. https://doi.org/10.1016/S1474-4422%2809%2970173-5.
2. Merwick A, Werring D. Posterior circulation ischaemic stroke. *BMJ*. 2014;348:g3175. https://doi.org/10.1136/bmj.g3175.
3. Caplan L, Chung CS, Wityk R, Glass T, Tapia J, Pazdera L, Chang HM, Dashe J, Chaves C, Vemmos K, et al. New England medical center posterior circulation stroke registry: I. Methods, data base, distribution of brain lesions, stroke mechanisms, and outcomes. *J Clin Neurol*. 2005;1:14–30. https://doi.org/10.3988/jcn.2005.1.1.14.
4. Archer CR, Horenstein S. Basilar artery occlusion: clinical and radiological correlation. *Stroke*. 1977;8:383–390. https://doi.org/10.1161/01.str.8.3.383.
5. Brandt T, Von Kummer R, Muller-Kuppers M, Hacke W. Thrombolytic therapy of acute basilar artery occlusion: variables affecting recanalization and outcome. *Stroke*. 1996;27:875–881. https://doi.org/10.1161/01.STR.27.5.875.
6. Edlow JA, Newman-Toker DE, Savitz SI. Diagnosis and initial management of cerebellar infarction. *Lancet Neurol*. 2008;7:951–964. https://doi.org/10.1016/S1474-4422(08)70216-3.
7. Ntaios G, Spengos K, Vemmou AM, Savvari P, Koroboki E, Stranjalis G, Vemmos K. Long-term outcome in posterior cerebral artery stroke. *Eur J Neurol*. 2011;18:1074–1080. https://doi.org/10.1111/j.1468-1331.2011.03384.x.
8. Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, de la Ossa NP, Strbian D, Tsivgoulis G, Turc G. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6. https://doi.org/10.1177/2396987321989865. I-LXII.
9. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho TH, Fazekas F, Fiehler J, et al. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 2018;379:611–622. https://doi.org/10.1056/NEJMoa1804355.
10. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, Levi CR, Hsu C, Kleinig TJ, Fatar M, et al. Extending thrombolysis to 4.5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet*. 2019;394:139–147. https://doi.org/10.1016/S0140-6736(19)31053-0.
11. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. https://doi.org/10.1016/S0140-6736(16)00163-X.
12. Marnat G, Kaesmacher J, Buetikofer L, Sibon I, Saleme S, Pop R, Henon H, Michel P, Mazighi M, Kulcsar Z, et al. Interaction between intravenous thrombolysis and clinical outcome between slow and fast progressors undergoing mechanical thrombectomy: a post-hoc analysis of the SWIFT-DIRECT trial. *J Neurointerv Surg*. 2023;16:45–52. https://doi.org/10.1136/jnis-2023-020113.
13. Mitchell PJ, Yan B, Churilov L, Dowling RJ, Bush S, Nguyen T, Campbell BCV, Donnan GA, Miao Z, Davis SM. DIRECT-SAFE: a randomized controlled trial of DIRECT endovascular clot retrieval versus standard bridging therapy. *J Stroke*. 2022;24:57–64. https://doi.org/10.5853/jos.2021.03475.
14. Jovin TG, Li C, Wu L, Wu C, Chen J, Jiang C, Shi Z, Gao Z, Song C, Chen W, et al. Trial of thrombectomy 6 to 24 hours after stroke due to basilar-artery occlusion. *N Engl J Med*. 2022;387:1373–1384. https://doi.org/10.1056/NEJMoa2207576.
15. Tao C, Nogueira RG, Zhu Y, Sun J, Han H, Yuan G, Wen C, Zhou P, Chen W, Zeng G, et al. Trial of endovascular treatment of acute basilar-artery occlusion. *N Engl J Med*. 2022;387:1361–1372. https://doi.org/10.1056/NEJMoa2206317.
16. Langezaal LCM, Van Der Hoeven EJRJ, Mont'Alverne FJA, De Carvalho JJF, Lima FO, Dippel DWJ, Van Der Lugt A, Lo RTH, Boiten J, Lycklama ANGJ, et al. Endovascular therapy for stroke due to basilar-artery occlusion. *N Engl J Med*. 2021;384:1910–1920. https://doi.org/10.1056/NEJMoa2030297.
17. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160. https://doi.org/10.1136/bmj.n160.
18. Wells GA, SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Ottawa Health Res Inst Web site*. 2014;7.
19. Higgins JPTLT, Deeks JJ. Chapter 6: choosing effect measures and computing estimates of effect. In: Higgins JPTTJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. Cochrane; 2022.
20. Yan S, Zhou Y, Zhao Y, Wang F, Tao A, Zhou L, Pan M, Zhong G, Hu L, Jiang X, et al. Effect of imaging markers on reperfusion therapy in basilar artery occlusion. *Ann Neurol*. 2022;92:97–106. https://doi.org/10.1002/ana.26376.
21. Dias FA, Alessio-Alves FF, Castro-Afonso LH, Cougo PT, Barreira CMA, Camilo MR, Nakiri GS, Abud DG, Pontes-Neto OM. Clinical outcomes of patients with acute basilar artery occlusion in Brazil: an observational study. *J Stroke Cerebrovasc Dis*. 2017;26:2191–2198. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.04.043.
22. Yang Y, Wang A, Zhao X, Wang C, Liu L, Zheng H, Wang Y, Cao Y, Wang Y. The Oxfordshire Community Stroke Project classification system predicts clinical outcomes following intravenous thrombolysis: a prospective cohort study. *Ther Clin Risk Manag*. 2016;12:1049–1056. https://doi.org/10.2147/TCRM.S107053.
23. Taha NA, El Khawas H, Tork MA, Roushdy TM. Intravenous thrombolysis outcome in posterior vs anterior circulation stroke in a tertiary stroke center in Egypt. *Egypt J Neurol, Psychiatry Neurosurg*. 2021;57:73. https://doi.org/10.1186/s41983-021-00325-0.
24. Ritvonen J, Sairanen T, Silvennoinen H, Virtanen P, Salonen O, Lindsberg PJ, Strbian D. Outcomes and long-term mortality after basilar artery occlusion a cohort with up to 20-year follow-up. *Eur J Neurol*. 2020. https://doi.org/10.1111/ene.14628.
25. Forster A, Gass A, Kern R, Griebe M, Hennerici MG, Szabo K. Thrombolysis in posterior circulation stroke: stroke subtypes and patterns, complications and outcome. *Cerebrovasc Dis*. 2011;32:349–353. https://doi.org/10.1159/000330346.
26. Zhu X, Wang N, Lin H, Zhang P, Chen L, Zhang M, Deng B, Wu T. Safety and efficacy of intravenous thrombolytic therapy in patients with acute posterior circulation stroke: a single-center study. *J Stroke Cerebrovasc Dis*. 2020;29, 104537. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104537.
27. Macha K, Hoelter P, Siedler G, Wang R, Knott M, Stoll S, Engelhorn T, Doerfler A, Schwab S, Muhlen I, et al. IV-Thrombolysis in ischemic stroke with unknown time of onset-safety and outcomes in posterior vs. anterior circulation stroke. *Front Neurol*. 2021;12, 692067. https://doi.org/10.3389/fneur.2021.692067.
28. Huang Q, Song HQ, Ma QF, Song XW, Wu J. Effects of time delays on the therapeutic outcomes of intravenous thrombolysis for acute ischemic stroke in the posterior circulation: an observational study. *Brain Behav*. 2019;9:e01189. https://doi.org/10.1002/brb3.1189.
29. Keselman B, Gdovinova Z, Jatuzis D, Melo TPE, Vilionskis A, Cavallo R, Frol S, Jurak L, Koyuncu B, Nunes AP, et al. Safety and outcomes of intravenous thrombolysis in posterior versus anterior circulation stroke: results from the safe implementation of treatments in stroke registry and meta-analysis. *Stroke*. 2020;51:876–882. https://doi.org/10.1161/STROKEAHA.119.027071.
30. Breuer L, Huttner HB, Jentsch K, Blinzler C, Winder K, Engelhorn T, Kohrmann M. Intravenous thrombolysis in posterior cerebral artery infarctions. *Cerebrovasc Dis*. 2011;31:448–454. https://doi.org/10.1159/000323253.
31. Sarikaya H, Arnold M, Engelter ST, Lyrer PA, Mattle HP, Georgiadis D, Bonati LH, Fluri F, Fischer U, Findling O, et al. Outcomes of intravenous thrombolysis in posterior versus anterior circulation stroke. *Stroke*. 2011;42:2498–2502. https://doi.org/10.1161/STROKEAHA.110.607614.
32. Schonewille WJ, Algra A, Serena J, Molina CA, Kappelle LJ. Outcome in patients with basilar artery occlusion treated conventionally. *J Neurol Neurosurg Psychiatry*. 2005;76:1238–1241. https://doi.org/10.1136/jnnp.2004.049924.
33. Voetsch B, DeWitt LD, Pessin MS, Caplan LR. Basilar artery occlusive disease in the New England medical center posterior circulation registry. *Arch Neurol*. 2004;61:496–504. https://doi.org/10.1001/archneur.61.4.496.
34. Mehler MF. The rostral basilar artery syndrome: diagnosis, etiology, prognosis. *Neurology*. 1989;39:9–16. https://doi.org/10.1212/wnl.39.1.9.
35. Hacke W, Zeumer H, Ferbert A, Bruckmann H, del Zoppo GJ. Intra-arterial thrombolytic therapy improves outcome in patients with acute vertebrobasilar occlusive disease. *Stroke*. 1988;19:1216–1222. https://doi.org/10.1161/01.str.19.10.1216.
36. Bruckmann H, Ferbert A, del Zoppo GJ, Hacke W, Zeumer H. Acute vertebral-basilar thrombosis. Angiologic-clinical comparison and therapeutic implications. *Acta Radiol Suppl*. 1986;369:38–42.
37. Strambo D, Bartolini B, Beaud V, Nannoni S, Marto JP, Sirimarco G, Dunet V, Saliou G, Michel P. Thrombectomy and thrombolysis of isolated posterior cerebral artery occlusion: cognitive, visual and disability outcomes [published correction appears in 5th European Stroke Organisation Conference, ESOC 2019. Milan Italy.]. *Eur Stroke J*. 2019;4:501–502. https://doi.org/10.1177/2396987319845581.
38. Tohgi H, Takahashi S, Chiba K, Hirata Y. Cerebellar infarction. Clinical and neuroimaging analysis in 293 patients. The Tohoku Cerebellar Infarction Study Group. *Stroke*. 1993;24:1697–1701. https://doi.org/10.1161/01.str.24.11.1697.
39. Salerno A, Strambo D, Marie G, Costamagna G, Dunet V, Saliou G, Michel P. Best revascularisation approach for posterior circulation strokes with isolated vertebral artery occlusion: design of the 'bravo' study [published correction appears in 8th European Stroke Organisation Conference. Lyon France.]. *Eur Stroke J*. 2022;7:551–552. https://doi.org/10.1177/23969873221094907.
40. Demel SL, Broderick JP. Basilar occlusion syndromes: an update. *Neurohospitalist*. 2015;5:142–150. https://doi.org/10.1177/1941874415583847.
41. Nguyen T, Koroshetz WJ. Intensive care management of ischemic stroke. *Curr Neurol Neurosci Rep*. 2003;3:32–39. https://doi.org/10.1007/s11910-003-0034-9.
42. Lindsberg PJ, Mattle HP. Therapy of basilar artery occlusion: a systematic analysis comparing intra-arterial and intravenous thrombolysis. *Stroke*. 2006;37:922–928. https://doi.org/10.1161/01.STR.0000202582.29510.6b.
43. Baird TA, Muir KW, Bone I. Basilar artery occlusion. *Neurocrit Care*. 2004;1:319–329. https://doi.org/10.1385/NCC:1:3:319.

44. Lindsberg PJ, Sairanen T, Strbian D, Kaste M. Current treatment of basilar artery occlusion. *Ann N Y Acad Sci*. 2012;1268:35–44. https://doi.org/10.1111/j.1749-6632.2012.06687.x.
45. Sairanen T, Strbian D, Soinne L, Silvennoinen H, Salonen O, Artto V, Koskela I, Happola O, Kaste M, Lindsberg PJ. Intravenous thrombolysis of basilar artery occlusion: predictors of recanalization and outcome. *Stroke*. 2011;42:2175–2179. https://doi.org/10.1161/STROKEAHA.110.605584.
46. Sheng K, Tong M. Therapy for acute basilar artery occlusion: a systematic review and meta-analysis. *F1000Res*. 2019;8:165. https://doi.org/10.12688/f1000research.18042.1.
47. Strbian D, Sairanen T, Silvennoinen H, Salonen O, Kaste M, Lindsberg PJ. Thrombolysis of basilar artery occlusion: impact of baseline ischemia and time. *Ann Neurol*. 2013;73:688–694. https://doi.org/10.1002/ana.23904.
48. Strbian D, Sairanen T, Silvennoinen H, Salonen O, Lindsberg PJ. Intravenous thrombolysis of basilar artery occlusion: thrombus length versus recanalization success. *Stroke*. 2014;45:1733–1738. https://doi.org/10.1161/STROKEAHA.114.004884.