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## Utility of Intravenous Alteplase Prior to Endovascular Stroke Treatment: A Systematic Review and Meta-analysis of RCTs

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## **Abstract**

**Objective:** To provide a critical appraisal on the evidence from randomized-controlled clinical trials (RCTs) on the utility of direct endovascular treatment (dEVT) compared to the combination of endovascular treatment preceded by intravenous thrombolysis (bridging therapy, BT) for patients with acute large vessel occlusion (LVO).

**Methods:** Eligible RCTs were identified by searching Medline and Scopus. We calculated the corresponding odds ratios (ORs) and 95% confidence intervals (95%CI) and pooled estimates using random-effects models. The primary outcome was the probability of modified Rankin scale (mRS) score of 0-2 at 3 months.

**Results:** We included 3 studies comprising 1092 patients. No difference between dEVT and BT groups was detected for the outcomes of mRS 0-2 (OR=1.08,95%CI:0.85-1.38; adjusted OR=1.11, 95%CI:0.76-1.63), mRS 0-1 (OR=1.10, 95%CI:0.84-1.43; adjusted OR=1.16, 95%CI:0.84-1.61) and functional improvement at 3 months (common OR=1.08, 95%CI:0.88-1.34; adjusted common OR=1.09, 95%CI:0.86-1.37). Patients receiving dEVT had significantly lower likelihood of successful recanalization prior to the endovascular procedure compared to BT (OR=0.37, 95%CI:0.18-0.77). Patients receiving dEVT had lower intracranial bleeding rates compared to those receiving BT (OR=0.67, 95%CI:0.49-0.92), however, without significant difference in the probability of symptomatic intracranial hemorrhage. No differences in all-cause mortality, serious adverse events or procedural complications between the two groups were uncovered.

**Conclusions:** We detected no differences in functional outcomes of IV thrombolysis eligible patients with an acute LVO receiving dEVT compared to BT. Since uncertainty for most endpoints remains large and the available data is not able to exclude the possibility of overall benefit or harm, further RCTs are needed.

## **Introduction**

The safety and efficacy of intravenous thrombolysis (IVT) for patients with large vessel occlusion (LVO) who are also eligible for endovascular stroke treatment has been questioned.<sup>1</sup> Direct

endovascular thrombectomy (dEVT), bypassing the administration of any intravenous thrombolytic agent, has been suggested as an alternative therapeutic approach to the combination of IVT followed by endovascular treatment for acute ischemic stroke (AIS) patients who are eligible for both treatment modalities and present at a site that can offer prompt endovascular treatment.<sup>2, 3</sup> The hypothesis that dEVT is a non-inferior option to the current standard of care combination of IVT and endovascular thrombectomy, referred also as bridging therapy (BT), has been evaluated in the setting of multiple observational studies<sup>4</sup> and recently published randomized-controlled clinical trials (RCTs).<sup>5-7</sup>

In the light of the recently published RCTs<sup>5-7</sup> we performed a systematic review and meta-analysis to provide a critical appraisal on the current evidence on the relative efficacy and safety of dEVT compared to BT for AIS patients with LVO eligible for both therapeutic pathways presenting within 4.5 hours from stroke onset.

## Methods

The present systematic review and meta-analysis is reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement. Our review protocol has not been published or registered.

We searched Medline and Scopus on January 20, 2021 for published RCTs comparing dEVT with BT for the treatment of patients with AIS. The following combination of keywords was used in both database searches: "endovascular thrombectomy", "mechanical thrombectomy", "intravenous thrombolysis", "tissue plasminogen activator", "alteplase", "tenecteplase", "ischemic stroke", "cerebral ischemia", "large vessel occlusion". Only publications in English were considered and the following filters were applied: Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Multicenter Study, Pragmatic Clinical Trial, Randomized Controlled Trial. All observational studies and RCTs not randomizing patients according to IVT administration prior to the endovascular procedure were excluded. We assessed the risk of bias for relevant domains in each included study with the Cochrane Collaboration tool and evaluated the quality of summary evidence for each outcome of interest using the recommendations from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Literature search, data extraction and quality assessment was performed by three independent authors (AHK, LP, MS). All emerging conflicts were resolved after discussion with a tie-breaking

author (GT). The primary efficacy outcome of interest was the probability of modified Rankin Scale (mRS) score of 2 or less at 3 months. Secondary efficacy outcomes of interest included the probability of: 1. excellent outcome at 3-months (defined as mRS scores of 0 or 1), 2. functional improvement at 3-months (assessed with ordinal logistic regression analysis on the per 1-point decline in the ordinal mRS score [range, 0–6]), 3. successful recanalization prior to the endovascular procedure amending its performance, 4. successful recanalization after the endovascular procedure (according to the definition used in each study), 5. difference in time from randomization to groin puncture between patients receiving dEVT or BT. The primary safety outcome of interest was the probability of all-cause mortality at 3-months. Secondary safety outcomes of interest included the probability of 1. symptomatic intracranial hemorrhage (ICH; according to the definition used in each study), 2. any ICH, 3. serious adverse events, 4. any procedural complication, 5. vessel dissection, 6. puncture site complications, 7. contrast extravasation in follow-up scan.

For each outcome of interest we extracted or calculated the unadjusted odds ratios (ORs) and corresponding 95% confidence intervals (95%CI). All adjusted ORs and corresponding 95% CIs were extracted as provided by each individual study. For continuous outcomes reported in median values and corresponding interquartile ranges, we estimated the sample mean and standard deviation using the quantile estimation method.<sup>8</sup> Study estimates were pooled under the random-effects model. Heterogeneity was assessed with the  $I^2$  and Cochran Q statistics. Number needed to treat (NNT) and number needed to harm (NNH) were calculated using the formula  $NNT/NNH=1/[(1-RR) \times \text{outcome rate in the BT group}]$ .<sup>9</sup>

## Results

Literature search and study identification process is outlined in Figure 1. After excluding non-RCTs,<sup>10-12</sup> we identified 3 RCTs including a total of 1092 patients (Table 1).<sup>5-7</sup> For DIRECT-MT we highlight the risk of performance bias due to the difference in the percentages of patients allocated to the BT (9.4%) and dEVT (5.2%) arms in whom endovascular treatment was ultimately not performed. In the same study,<sup>6</sup> 9.1% and 1.2% of the patients allocated to the BT group either did not receive full-dose or any alteplase, respectively (Figure 2).

An overview of the efficacy endpoints analyses is provided in Table 2. The variables used for adjusting associations reported in each study are presented in Table 1. No difference between dEVT

and BT groups was detected for the outcomes of mRS 0-2 (unadjusted OR=1.08, 95% CI: 0.85-1.38,  $I^2=0\%$ , p for Cochran Q=0.57; adjusted OR=1.11, 95% CI: 0.76-1.63;  $I^2=28\%$ , p for Cochran Q=0.24), mRS 0-1 (unadjusted OR=1.10, 95% CI: 0.84-1.43,  $I^2=0\%$ , p for Cochran Q=0.51; adjusted OR=1.16, 95% CI: 0.84-1.61,  $I^2=0\%$ , p for Cochran Q=0.52) and functional improvement per 1-point increase in the mRS scale at 3 months (unadjusted common OR=1.08, 95% CI: 0.88-1.34,  $I^2=0\%$ , p for Cochran Q=0.85; adjusted common OR=1.09, 95% CI: 0.86-1.37,  $I^2=0\%$ , p for Cochran Q=0.84). Although no difference in the probability of successful recanalization after the end of the endovascular procedure was found between the two groups (unadjusted OR=0.77, 95% CI: 0.54-1.08,  $I^2=0\%$ , p for Cochran Q=0.56), patients allocated to receive dEVT had significantly lower likelihood of successful recanalization prior the initiation of endovascular thrombectomy compared to those receiving intravenous alteplase (OR=0.37, 95% CI: 0.18-0.77, NNT=33 for BT,  $I^2=0\%$ , p for Cochran Q=0.79). No difference in the elapsed time from randomization to groin-puncture was uncovered between patients randomized to dEVT or BT (mean difference= -1.67 minutes, 95% CI: -4.13 to 0.79,  $I^2=0\%$ , p for Cochran Q=0.71).

Analyses on the safety endpoints are summarized in Table 3. No difference between the two groups was uncovered in the likelihood of 3-month mortality (unadjusted OR=0.93, 95% CI: 0.68-1.29,  $I^2=0\%$ , p for Cochran Q=0.99). Patients receiving dEVT had lower intracranial bleeding rates compared to those receiving BT (unadjusted OR=0.67, 95% CI: 0.49-0.92, NNH=11 for BT,  $I^2=30\%$ , p for Cochran Q=0.24). There was no difference in the odds of symptomatic intracranial hemorrhage after the endovascular procedure (unadjusted OR=0.75, 95% CI: 0.45-1.25;  $I^2=0\%$ , p for Cochran Q=0.93). Also, no difference was found in the probability of any serious adverse event (unadjusted OR=1.05, 95% CI: 0.80-1.40,  $I^2=0\%$ , p for Cochran Q=0.56) or procedural complication (unadjusted OR=0.83, 95% CI: 0.49-1.40,  $I^2=56\%$ , p for Cochran Q=0.13), including vessel dissection (unadjusted OR=1.37, 95% CI: 0.47-3.97,  $I^2=0\%$ , p for Cochran Q=0.37) or puncture access site complication (unadjusted OR=0.54, 95% CI: 0.04-6.43,  $I^2=58\%$ , p for Cochran Q=0.12) between the two groups. Contrast extravasation in follow-up scan was detected at similar rates between the dEVT and BT groups (unadjusted OR=0.81, 95% CI: 0.45-1.47,  $I^2=0\%$ , p for Cochran Q=0.47). From all the aforementioned efficacy and safety analyses evidence of heterogeneity was only present in the analyses of procedural ( $I^2=56\%$ ) and puncture access complications ( $I^2=58\%$ ).

## Discussion

Our meta-analysis detected no difference in functional outcomes between direct thrombectomy and combination with bridging IV thrombolysis in Asian stroke patients with LVO. Intravenous alteplase pretreatment was associated with a higher likelihood of successful reperfusion prior to endovascular thrombectomy and a higher probability of intracranial bleeding after endovascular treatment, without increasing the risk for symptomatic intracranial hemorrhage.

Effect estimates from available RCTs, presented in the current systematic review and meta-analysis, when compared to those provided by observational studies<sup>4</sup> raise concerns for heterogeneity in inclusion criteria and the possibility for selection bias within published cohorts. As an example, the lack of treatment delays for patients allocated to receive BT in RCTs (Table 2) contradicts previous observational studies associating IVT administration with prolongation of the time to initiate an endovascular procedure.<sup>10</sup> Although hemorrhagic infarction type 2 and parenchymal hematoma type 2 after endovascular stroke thrombectomy have previously been associated with worse functional outcomes,<sup>13</sup> the increased likelihood of intracranial bleeding of any type found in patients allocated to BT compared to dEVT did not translate into worse functional outcomes in the included RCTs.<sup>5-7</sup>

The issue of generalizability of the evidence from individual RCTs<sup>5-7</sup> and the results from the current meta-analysis beyond the Asian population deserves particular attention. The prevalence of intracranial atherosclerosis is known to be higher in Asians, including the Chinese and Japanese populations.<sup>14</sup> Taking into consideration the possibility for an increased attributable fraction of patients with LVO due to intracranial atherosclerosis in included RCTs<sup>5-7</sup> together with the less pronounced effect of thrombolysis in platelet-rich thrombi associated with atherosclerotic disease, as uncovered in experimental models,<sup>15</sup> it may be hypothesized that any beneficial effect of IVT in the BT arm could be significantly attenuated. Additionally, it should be kept in mind that alteplase is not reimbursed in China and this may introduce substantial selection bias in the BT group.<sup>16</sup>

Although in two of the trials (DEVT and DIRECT-MT) the non-inferiority margin was technically met,<sup>5,6</sup> the margins in all of the trials were overly generous and not selected using clinical reasoning based on the minimal clinically important difference, but rather estimated using the fixed-margin method.<sup>5-7</sup> Specifically, DIRECT-MT and SKIP pre-specified as statistical thresholds for noninferiority a common OR of 0.8 for the ordinal analysis of the mRS score at 90 days and an OR of 0.74 for the dichotomous outcome of favorable outcome (mRS of 0 to 2) at 90 days, respectively.<sup>6,7</sup> In

DEVT a difference  $\leq 10\%$  in the rates of functional independence (mRS of 0 to 2) at 90 days was used as the non-inferiority margin.<sup>5</sup> Based on the 1.3% and 5% non-inferiority margins, derived from two previous surveys of stroke experts to establish the minimally clinically important difference for stroke therapies and which were used in a previous meta-analysis comparing two thrombolytic agents in acute stroke treatment,<sup>17</sup> the pooled estimate of included RCTs justifies the non-inferiority claim only when using the less conservative margin of 5%, with none of the individual studies however being able to surpass either the 1.3% or 5% non-inferiority margins (Figure 3). Additionally, the early termination of one of the including trials poses the risk for overestimation in the reported effect sizes,<sup>5</sup> while the wide prediction intervals from the pooled analyses further highlight the increased uncertainty regarding true effect estimates and need for additional RCTs (Figure 3). The effect of IVT to induce successful reperfusion for patients presenting with acute LVOs, amending the need for endovascular treatment, has previously been acknowledged.<sup>18</sup>

Given that evidence are still inconclusive and cannot exclude the possibility of either benefit or harm, particularly for specific subgroups, additional trials are needed. Ongoing trials in Europe and Australia (MR CLEAN-NO IV, ISRCTN80619088; SWIFT-DIRECT, NCT03192332; DIRECT-SAFE, NCT03494920) will also determine whether these findings generalize to non-Asian patients. The results of currently published and ongoing trials can apply only to mothership patients, as BT should be the only option to consider for drip and ship patients.



## References

1. Fischer U, Kaesmacher J, Mendes Pereira V, et al. Direct Mechanical Thrombectomy Versus Combined Intravenous and Mechanical Thrombectomy in Large-Artery Anterior Circulation Stroke: A Topical Review. *Stroke*. 2017;48:2912-2918.
2. Katsanos AH, Tsivgoulis G. Is intravenous thrombolysis still necessary in patients who undergo mechanical thrombectomy? *Curr Opin Neurol*. 2019;32:3-12.
3. Fischer U, Kaesmacher J, Molina CA, Selim MH, Alexandrov AV, Tsivgoulis G. Primary Thrombectomy in tPA (Tissue-Type Plasminogen Activator) Eligible Stroke Patients With Proximal Intracranial Occlusions. *Stroke*. 2018;49:265-269.
4. Katsanos AH, Malhotra K, Goyal N, et al. Intravenous thrombolysis prior to mechanical thrombectomy in large vessel occlusions. *Ann Neurol*. 2019;86:395-406.
5. Zi W, Qiu Z, Li F, et al. Effect of Endovascular Treatment Alone vs Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke: The DEVT Randomized Clinical Trial. *JAMA*. 2021;325:234-243.
6. Yang P, Zhang Y, Zhang L, et al. Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke. *N Engl J Med*. 2020;382:1981-1993.
7. Suzuki K, Matsumaru Y, Takeuchi M, et al. Effect of Mechanical Thrombectomy Without vs With Intravenous Thrombolysis on Functional Outcome Among Patients With Acute Ischemic Stroke: The SKIP Randomized Clinical Trial. *JAMA*. 2021;325:244-253.
8. McGrath S, Zhao X, Steele R, Thombs BD, Benedetti A; DEPRESSion Screening Data (DEPRESSD) Collaboration. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Stat Methods Med Res*. 2020 Jan 30:962280219889080. doi: 10.1177/0962280219889080. Epub ahead of print.
9. Mendes D, Alves C, Batel-Marques F. Number needed to treat (NNT) in clinical literature: an appraisal. *BMC Med*. 2017;15:112.
10. Chalos V, LeCouffe NE, Uyttenboogaart M, et al. Endovascular Treatment With or Without Prior Intravenous Alteplase for Acute Ischemic Stroke. *J Am Heart Assoc*. 2019;8:e011592.
11. Coutinho JM, Liebeskind DS, Slater LA, et al. Combined Intravenous Thrombolysis and Thrombectomy vs Thrombectomy Alone for Acute Ischemic Stroke: A Pooled Analysis of the SWIFT and STAR Studies. *JAMA Neurol*. 2017;74:268-274.

12. Maingard J, Shvarts Y, Motyer R, et al. Outcomes of endovascular thrombectomy with and without bridging thrombolysis for acute large vessel occlusion ischaemic stroke. *Intern Med J.* 2019;49:345-351.
13. van Kranendonk KR, Treurniet KM, Boers AMM, et al. Hemorrhagic transformation is associated with poor functional outcome in patients with acute ischemic stroke due to a large vessel occlusion. *J Neurointerv Surg.* 2019;11:464-468
14. Feldmann E, Daneault N, Kwan E, et al. Chinese-white differences in the distribution of occlusive cerebrovascular disease. *Neurology.* 1990;40:1541-5.
15. Jang IK, Gold HK, Ziskind AA, et al. Differential sensitivity of erythrocyte-rich and platelet-rich arterial thrombi to lysis with recombinant tissue-type plasminogen activator. A possible explanation for resistance to coronary thrombolysis. *Circulation.* 1989;79:920-8.
16. Nogueira RG, Tsivgoulis G. Large Vessel Occlusion Strokes After the DIRECT-MT and SKIP Trials: Is the Alteplase Syringe Half Empty or Half Full? *Stroke.* 2020;51:3182-3186.
17. Burgos AM, Saver JL. Evidence that Tenecteplase Is Noninferior to Alteplase for Acute Ischemic Stroke: Meta-Analysis of 5 Randomized Trials. *Stroke.* 2019;50:2156-2162.
18. Tsivgoulis G, Katsanos AH, Schellinger PD, et al. Successful Reperfusion With Intravenous Thrombolysis Preceding Mechanical Thrombectomy in Large-Vessel Occlusions. *Stroke.* 2018;49:232-235.

**Table 1. Overview of included studies**

| Study name    | dEVT/ BT patients | Country (centers) | Median age (years) | Females (%) | Median NIHSS | Median ASPECTS | LVO (%)   | Alteplase dose (mg/kg) | sICH definiti on | Adjusted for   |
|---------------|-------------------|-------------------|--------------------|-------------|--------------|----------------|---|------------------------|------------------|--|
| DEVT [5]      | 116/ 118          | China (33)        | 70 (60-78)         | 44          | 16           | 8 (7-9)        | ICA: 15<br>M1-MCA: 82<br>M2-MCA: 2<br>Tandem: N/A | 0.9                    | HBC              | age, baseline NIHSS score, baseline ASPECTS, onset to randomization time, occlusion site |
| DIRECT-MT [6] | 326/ 328          | China (41)        | 69 (61-76)         | 44          | 17           | 9 (7-10)       | ICA: 35<br>M1-MCA: 52<br>M2-MCA: 11<br>Tandem: 10 | 0.9                    | HBC              | age, baseline NIHSS, onset to randomization time, baseline mRS, collateral status        |
| SKIP [7]      | 101/ 103          | Japan (23)        | 74 (67-80)         | 37          | 18           | 8 (6-9)        | ICA: 35<br>M1-MCA: 50<br>M2-MCA: 15<br>Tandem: 11 | 0.6                    | SITS-MOST        | N/A  |

NIHSS: National Institutes of Health Stroke Scale, ASPECTS: Alberta Stroke Program Early CT Score, LVO: large vessel occlusion, sICH: symptomatic intracranial hemorrhage, ICA: internal carotid artery, MCA: middle cerebral artery, HBC: Heidelberg bleeding classification, mRS: modified Rankin Scale score, SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study, N/A: not available

**Table 2.** Overview of the analyses on efficacy endpoints

| Outcomes                                   | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI)          | Anticipated absolute effects*       |   |
|--|-----------------------------|-----------------------------------|-----------------------------------|-------------------------------------|---|
|  |                             |                                   |                                   | Risk with BT                        | Risk difference with dEVT                                   |
| <b>Efficacy outcomes</b>                   |                             |                                   |                                   |                                     |   |
| mRS 0-2 at 3 months                        | 1092 (3 RCTs)               | ⊕⊕○○<br>LOW <sup>a,b</sup>        | <b>OR 1.08</b><br>(0.85 to 1.38)  | 428 per 1,000                       | <b>19 more per 1,000</b><br>(39 fewer to 80 more)           |
| mRS 0-2 at 3 months (adjusted)             | 888 (2 RCTs)                | ⊕○○○<br>VERY LOW <sup>a,b,d</sup> | <b>OR 1.11</b><br>(0.76 to 1.63)  | -                                   | -   |
| mRS 0-1 at 3 months                        | 1092 (3 RCTs)               | ⊕⊕○○<br>LOW <sup>a,b</sup>        | <b>OR 1.10</b><br>(0.84 to 1.43)  | 286 per 1,000                       | <b>20 more per 1,000</b><br>(34 fewer to 78 more)           |
| mRS 0-1 at 3 months (adjusted)             | 888 (2 RCTs)                | ⊕○○○<br>VERY LOW <sup>a,b,d</sup> | <b>OR 1.16</b><br>(0.84 to 1.61)  | -                                   | -   |
| Functional improvement at 3 months         | 1092 (3 RCTs)               | ⊕⊕○○<br>LOW <sup>a,b</sup>        | <b>cOR 1.08</b><br>(0.88 to 1.34) | -                                   | -   |
| Functional improvement 3 months (adjusted) | 888 (2 RCTs)                | ⊕○○○<br>VERY LOW <sup>a,b,d</sup> | <b>cOR 1.09</b><br>(0.86 to 1.37) | -                                   | -   |
| Successful recanalization before EVT       | 1095 (3 RCTs)               | ⊕⊕⊕○<br>MODERATE <sup>a</sup>     | <b>OR 0.37</b><br>(0.18 to 0.77)  | 49 per 1,000                        | <b>30 fewer per 1,000</b><br>(40 fewer to 11 fewer)         |
| Successful recanalization after EVT        | 1056 (3 RCTs)               | ⊕⊕○○<br>LOW <sup>a,b</sup>        | <b>OR 0.77</b><br>(0.54 to 1.08)  | 868 per 1,000                       | <b>33 fewer per 1,000</b><br>(88 fewer to 9 more)           |
| Randomization to puncture time             | 1094 (3 RCTs)               | ⊕⊕○○<br>LOW <sup>a,b</sup>        | -                                 | The mean time was <b>33 minutes</b> | <b>MD 1.67 minutes lower</b><br>(4.13 lower to 0.79 higher) |

\*expressed as the risk difference (with corresponding 95% CI) and based on the baseline risk in the BT group and the relative effect of dEVT

CI: confidence interval; OR: odds ratio; cOR: common odds ratio; MD: mean difference a. risk of selection and performance bias within studies, b. confidence intervals fail to exclude benefit or harm, d. effect estimate provide by two studies

**Table 3.** Overview of the analyses on safety endpoints

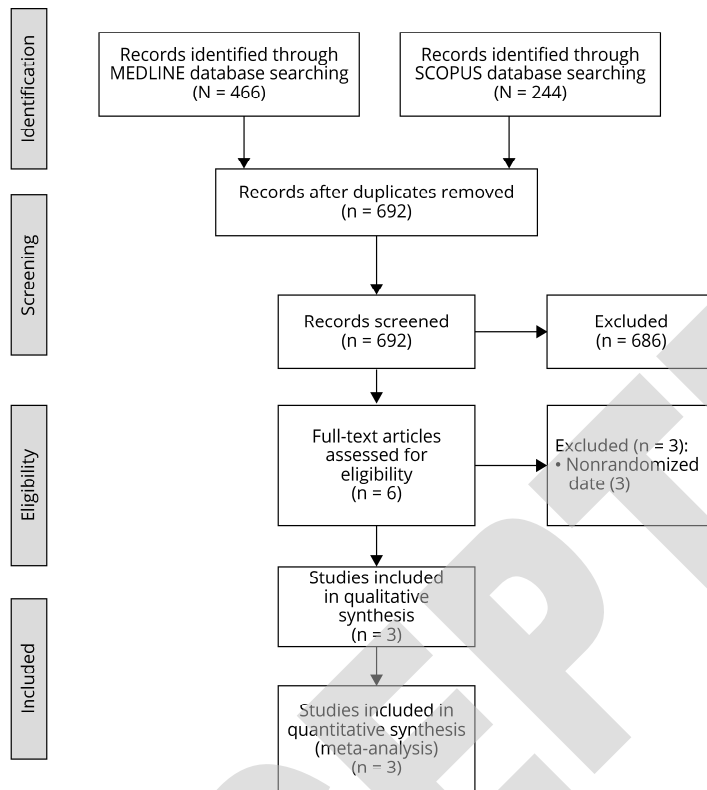
| Outcomes                       | № of participants (studies) | Certainty of the evidence (GRADE)   | Relative effect (95% CI)         | Anticipated absolute effects* |  |
|--------------------------------|-----------------------------|-------------------------------------|----------------------------------|-------------------------------|--|
|                                |                             |                                     |                                  | Risk with BT                  | Risk difference with dEVT                            |
| <b>Safety outcomes</b>         |                             |                                     |                                  |                               |  |
| All-cause mortality at 90 days | 1092 (3 RCTs)               | ⊕⊕○○<br>LOW <sup>a,b</sup>          | <b>OR 0.93</b><br>(0.68 to 1.29) | 168 per 1,000                 | <b>10 fewer per 1,000</b><br>(47 fewer to 39 more)   |
| Symptomatic ICH                | 1092 (3 RCTs)               | ⊕⊕○○<br>LOW <sup>a,b</sup>          | <b>OR 0.75</b><br>(0.45 to 1.25) | 66 per 1,000                  | <b>16 fewer per 1,000</b><br>(35 fewer to 15 more)   |
| Any ICH                        | 1092 (3 RCTs)               | ⊕⊕⊕○<br>MODERATE <sup>a</sup>       | <b>OR 0.67</b><br>(0.49 to 0.92) | 417 per 1,000                 | <b>93 fewer per 1,000</b><br>(158 fewer to 20 fewer) |
| Serious adverse events         | 890 (2 studies)             | ⊕⊕○○<br>LOW <sup>a,b,d</sup>        | <b>OR 1.05</b><br>(0.80 to 1.40) | 329 per 1,000                 | <b>11 more per 1,000</b><br>(47 fewer to 78 more)    |
| Any procedural complication    | 886 (2 RCTs)                | ⊕○○○<br>VERY LOW <sup>a,b,c,d</sup> | <b>OR 0.83</b><br>(0.49 to 1.40) | 213 per 1,000                 | <b>30 fewer per 1,000</b><br>(96 fewer to 62 more)   |
| Vessel dissection              | 886 (2 RCTs)                | ⊕⊕○○<br>LOW <sup>a,b,d</sup>        | <b>OR 1.37</b><br>(0.47 to 3.97) | 13 per 1,000                  | <b>5 more per 1,000</b><br>(7 fewer to 38 more)      |
| Puncture access complications  | 890 (2 RCTs)                | ⊕○○○<br>VERY LOW <sup>a,b,c,d</sup> | <b>OR 0.54</b><br>(0.04 to 6.43) | 16 per 1,000                  | <b>7 fewer per 1,000</b><br>(15 fewer to 77 more)    |
| Contrast extravasation         | 888 (2 RCTs)                | ⊕⊕○○<br>LOW <sup>a,b,d</sup>        | <b>OR 0.81</b><br>(0.45 to 1.47) | 61 per 1,000                  | <b>11 fewer per 1,000</b><br>(32 fewer to 26 more)   |

\*expressed as the risk difference (with corresponding 95% CI) and based on the baseline risk in the BT group and the relative effect of dEVT

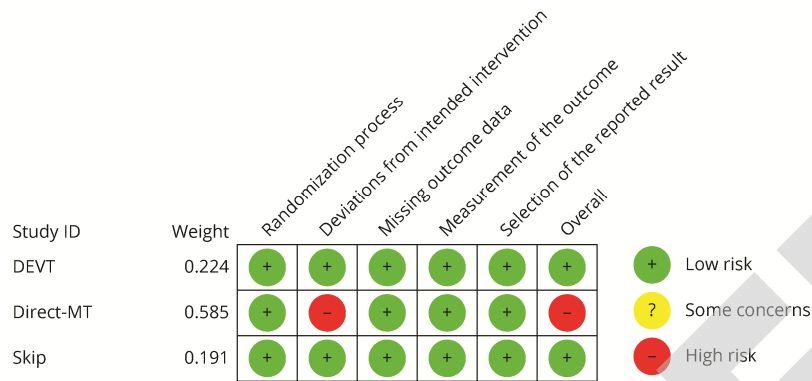
CI: confidence interval; OR: odds ratio; MD: mean difference a. risk of selection and performance bias within studies, b. confidence intervals fail to exclude benefit or harm, c. presence of heterogeneity between studies, d. effect estimate provide by two studies

## FIGURES

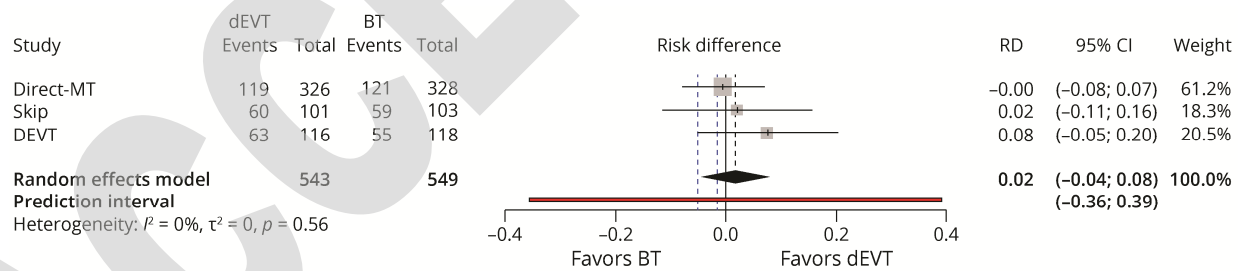
**Figure 1.** Flow chart on the selection of eligible studies



**Figure 2.** Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



**Figure 3.** Absolute risk difference on the outcome of modified Rankin Scale score of 2 or less at 3 months between patients randomized to direct endovascular treatment or endovascular treatment preceded by intravenous thrombolysis. The dashed blue vertical lines represent the minimally clinically important differences for stroke therapies set at 5% and 1.3% respectively.



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## Utility of Intravenous Alteplase Prior to Endovascular Stroke Treatment: A Systematic Review and Meta-analysis of RCTs

Aristeidis Katsanos, Guillaume Turc, Marios Psychogios, et al.

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