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Expedited recommendation on intravenous thrombolysis before mechanical thrombectomy in patients with acute ischaemic stroke and anterior circulation large vessel occlusion

Turc G, Tsivgoulis G, Audebert HJ, Boogarts H, Bhogal P, De Marchis GM, Fonseca AC, Khatri P, Mazighi M, Pérez de la Ossa N, Schellinger PD, Strbian D, Toni D, White P, Whiteley W, Zini A, van Zwam W, and Fiehler J

Guideline Webinar – 3 February 2022

Disclosures

Disclosures of the 18 module working group members are provided in Suppl. Table I of the Recommendations

Personal Intellectual Disclosures:

- Chairman of the ESO Guideline board
- Co-chairman of the 2019 ESO-ESMINT Guidelines on mechanical thrombectomy
- Co-chairman of the 2021 ESO Guidelines on intravenous thrombolysis

Financial Disclosures:

- Lecturing fees for Guerbet France

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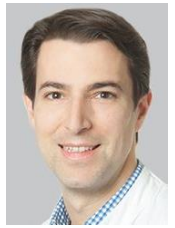

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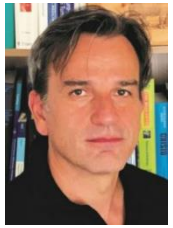

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Background

Do we still need IVT before MT in patients with large vessel occlusion?

In favour of direct MT

- IVT is associated with low rates of successful reperfusion before MT
- Risk of intracranial haemorrhage
- May delay MT
- Thrombus fragmentation
- Substantial costs

In favour of bridging therapy

- A minority of LVO patients recanalize early with IVT
- IVT may improve the rate of successful reperfusion after MT
- Fewer recanalization attempts?
- May reduce microvascular thrombosis
- Beneficial in patients with unsuccessful MT?

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Fischer U et al, Stroke 2017 & 2018; Seners P et al, Stroke 2016 & 2018; Tsivgoulis G et al, Stroke 2018; Desilles JP et al, Stroke 2015; Ospel JM et al, JNIS 2021; Rozes C et al, JNIS 2021

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Methodology

ESO Standard Operating Procedure

- Evidence-based recommendations
  - GRADE methodology
    - 2 PICO Questions: mothership, drip-and-ship
    - Rating of the importance of outcomes of interest
    - Systematic review and meta-analyses
    - Quality of evidence / Strength of recommendations
- Expert Consensus Statements
  - Secret ballot voting, Delphi method

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Steiner T et al, Eur Stroke J 2021 ;6(3):CXXII-CXXXIV

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PICO Question

Mothership, ≤4.5 hrs of symptom onset

PICO 1: For large vessel occlusion acute ischaemic stroke (≤ 4.5 hrs of symptom onset) patients **directly admitted to a thrombectomy capable centre** and eligible for both treatments, **does mechanical thrombectomy alone compared with intravenous thrombolysis plus mechanical thrombectomy** lead to:

a) a non-inferior proportion of patients with **good outcome (mRS 0-2) at 90 days**?
b) non-inferior or better results on other efficacy outcomes (whole range of the mRS; mRS 0-1; successful reperfusion)?
c) a reduction in the risk of adverse events (mortality at 90 days, intracranial haemorrhage)?

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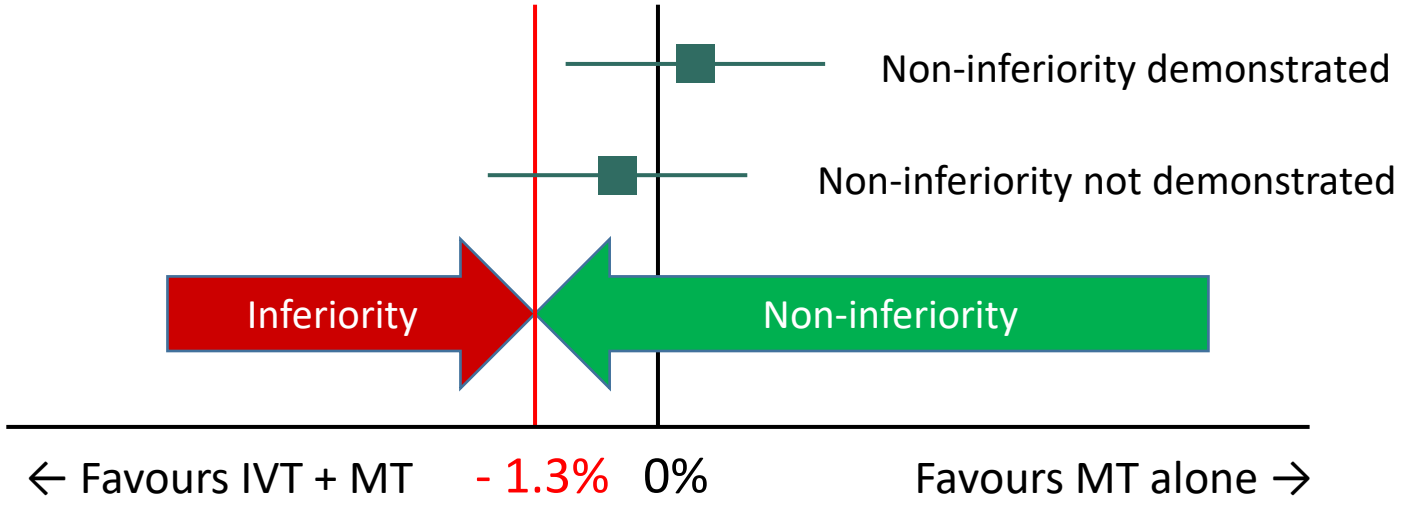
Methodology

Pre-defined non-inferiority margin

- Primary endpoint: Pooled unadjusted ‘Risk’ Difference (%) in mRS 0-2 at 90 days
- Random-effects meta-analysis

- Secret ballot voting: non-inferiority margin: 1.3% (range: 1.0% to 5.0%)



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Randomized controlled clinical trials

Mothership, ≤4.5 hrs of symptom onset

Trial	Status	N	Location	Non-inferiority margin	Conclusion of non inferiority
DIRECT-MT	Published	654	China	Relative, cOR 0.80	Yes
DEVT	Published	234	China	Absolute, 10% mRS 0-2	Yes
SKIP	Published	204	Japan	Relative, OR 0.74 mRS 0-2	No
MR CLEAN No IV	Published	539	Europe	Relative, cOR 0.80	No
SWIFT DIRECT	Results presented	404	Europe & North America	Absolute, 12% mRS 0-2	No
DIRECT-SAFE	Results presented	293	Oceania & Asia	Absolute, 10% mRS 0-2	No

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LeCouffe N et al, NEJM 2021; Fischer U et al, ESOC 2021; Mitchell PJ et al, WSC 2021

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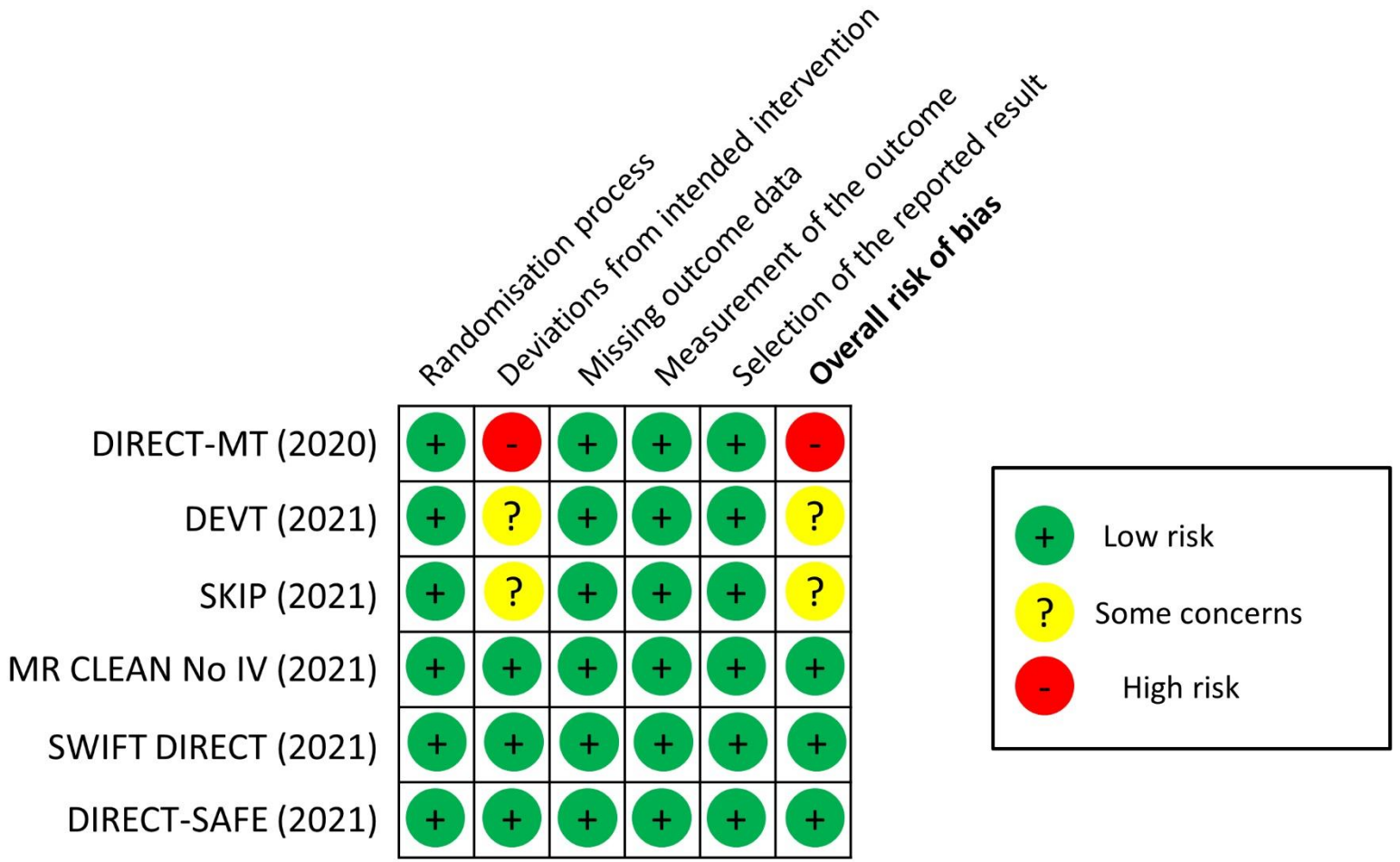
Quality of evidence

Outcome: mRS score at 90 days



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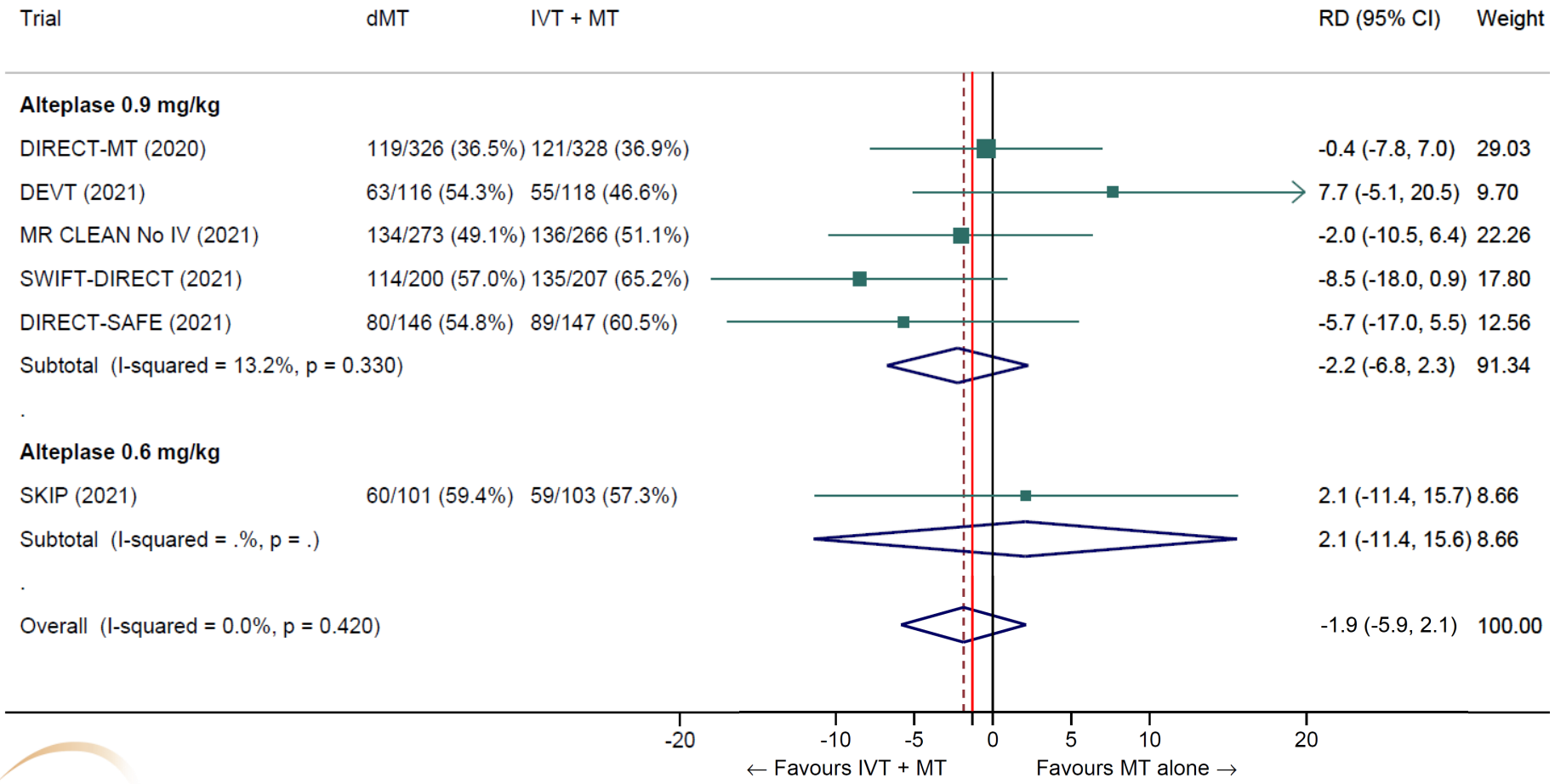
Direct MT vs. IVT plus MT

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



Unadj. RD -1.9% (95% CI -5.9% to 2.1%)

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Direct MT vs. IVT plus MT

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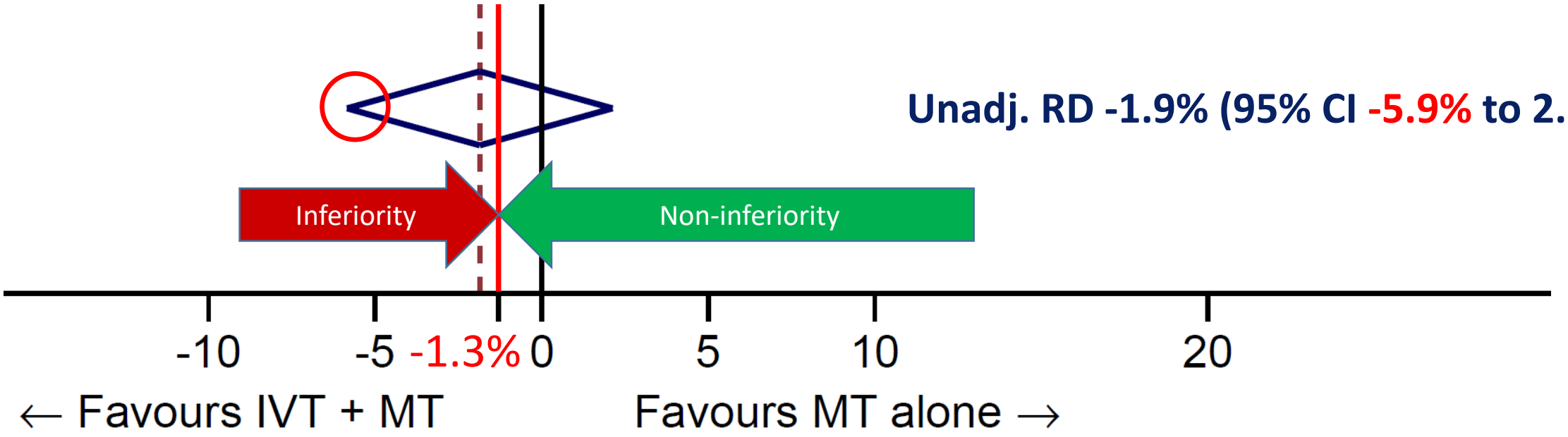

Unadj. RD -1.9% (95% CI -5.9% to 2.1%)

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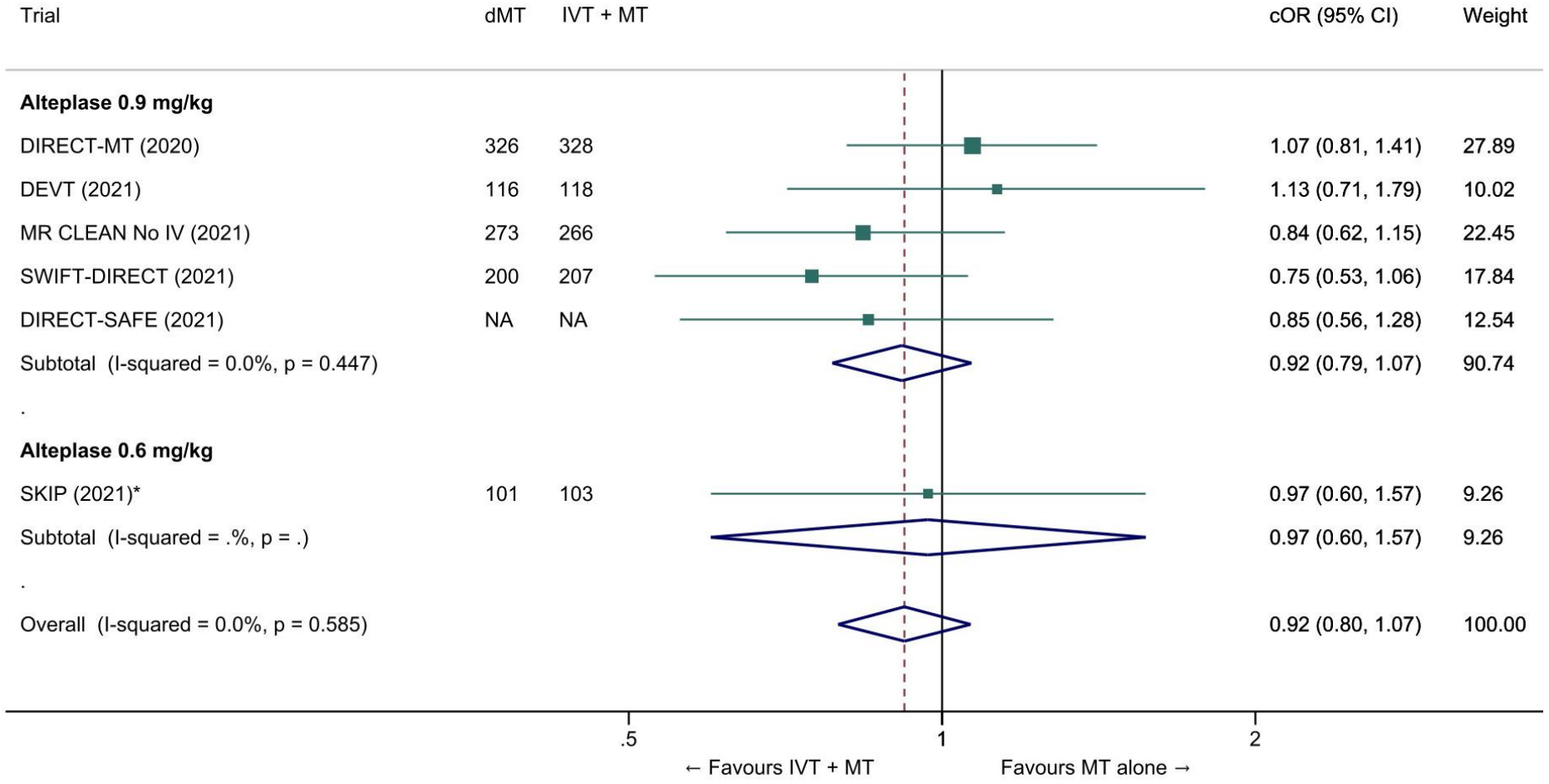
Direct MT vs. IVT plus MT

Reduced disability (whole range of the mRS at 90 days)



Adj. common OR 0.92 (95% CI 0.80 to 1.07)

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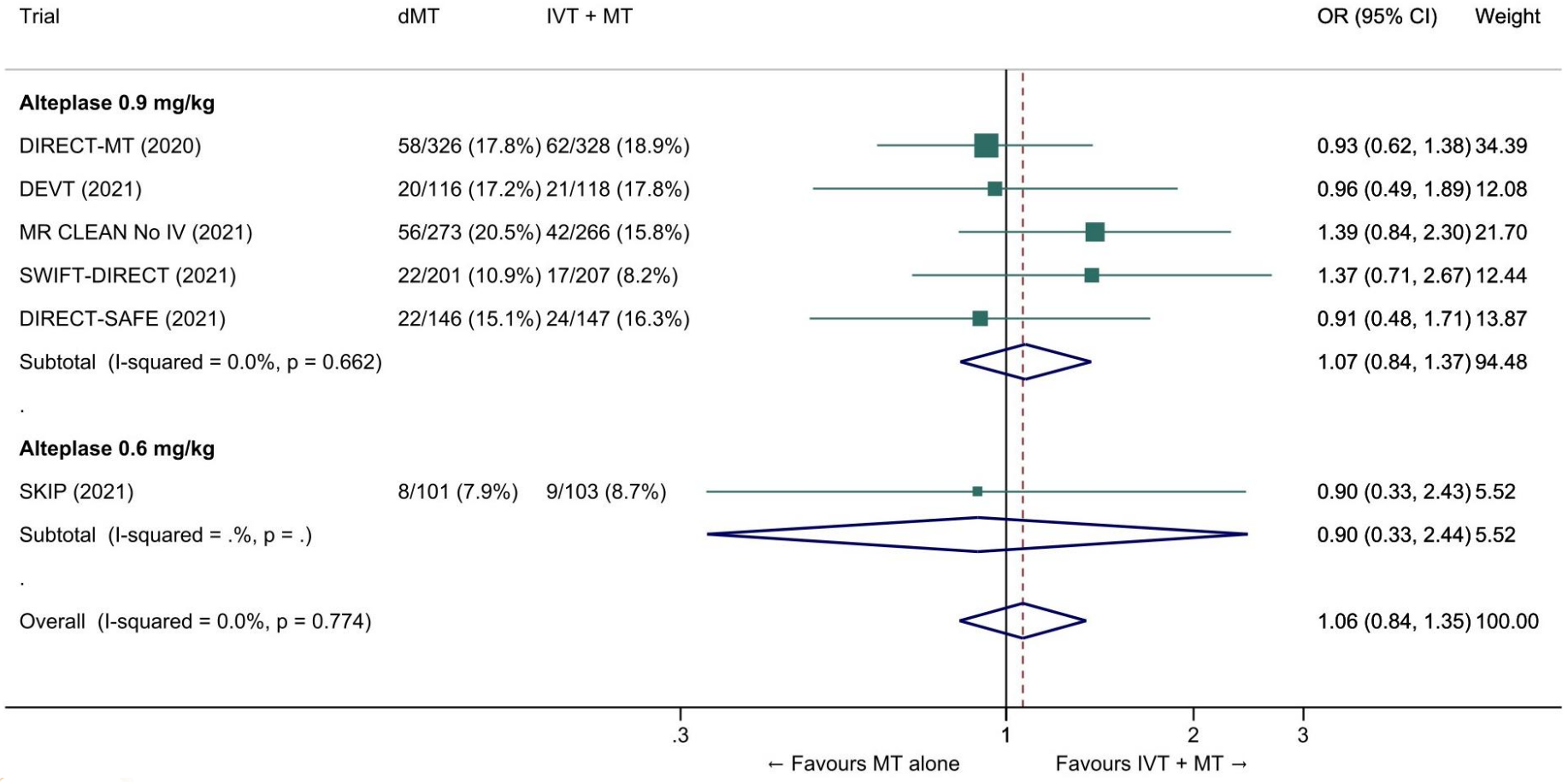
Direct MT vs. IVT plus MT

Death at 90 days



Unadj. OR 1.06 (95% CI 0.84 to 1.35)

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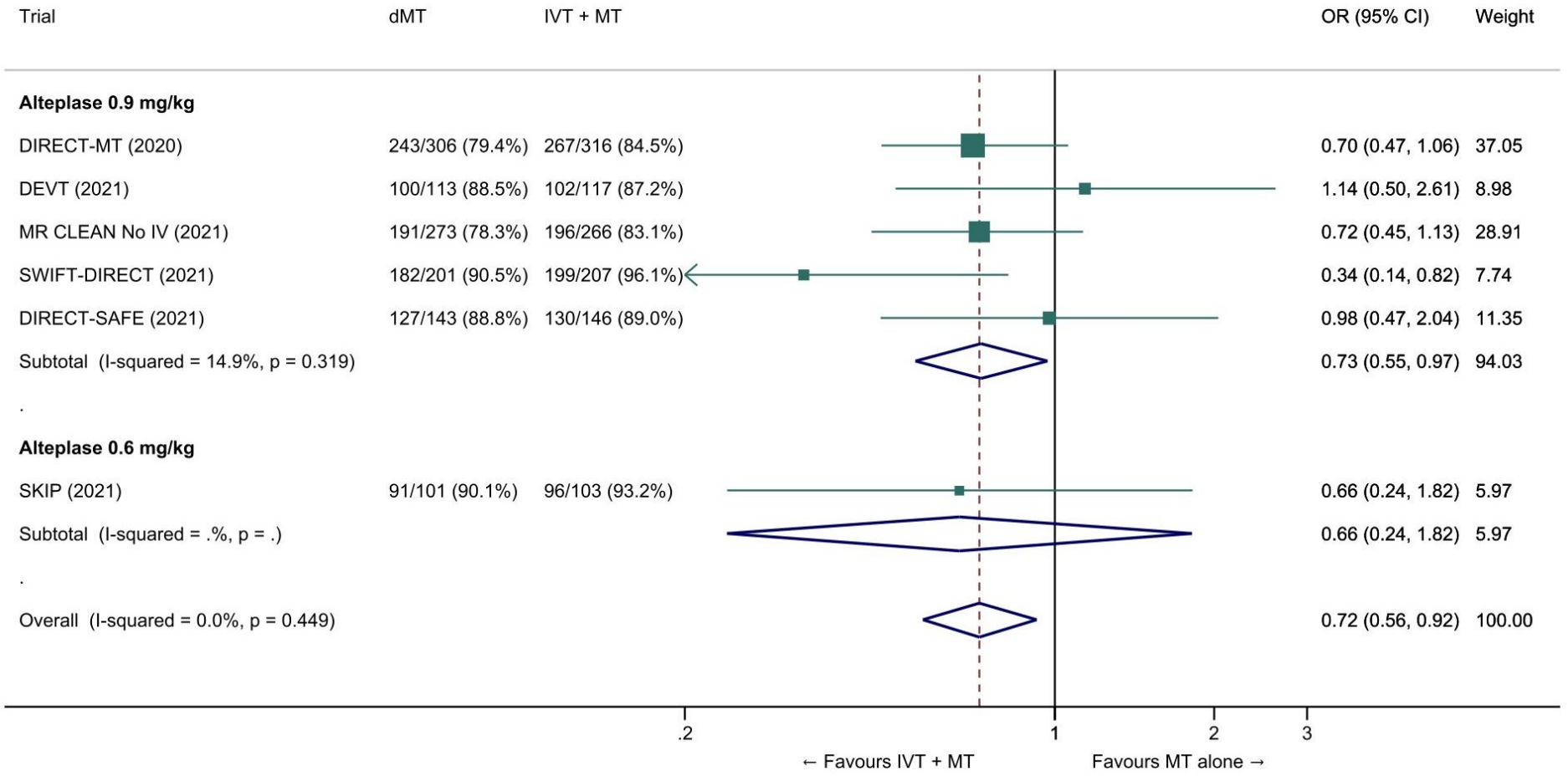
Direct MT vs. IVT plus MT

Succesful reperfusion (mTICI ≥2b) at the end of the endovascular procedure



Unadj. OR 0.72 (95% CI 0.56 to 0.92)

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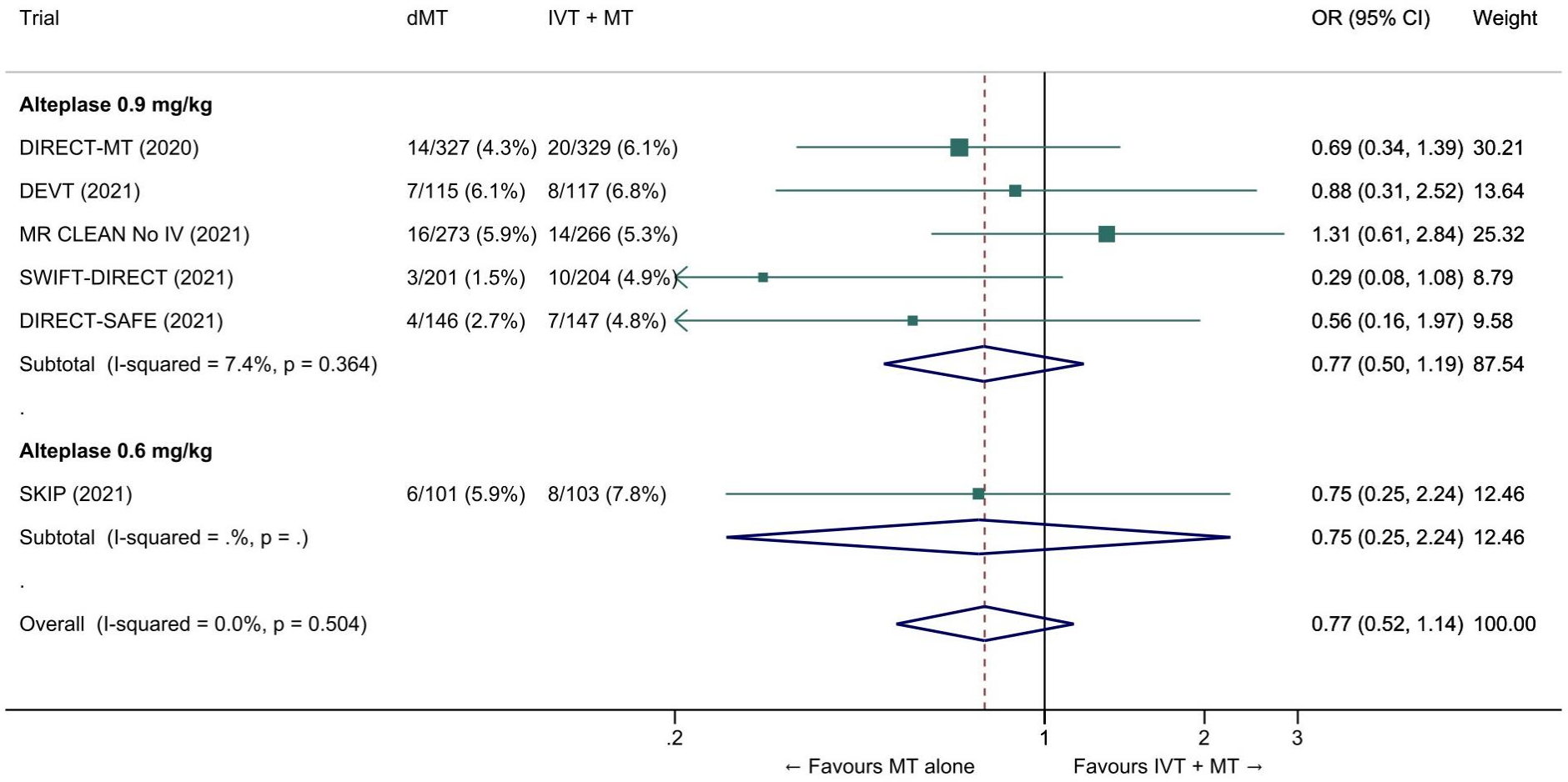
Direct MT vs. IVT plus MT

Symptomatic intracranial haemorrhage



Unadj. OR 0.77 (95% CI 0.52 to 1.14)

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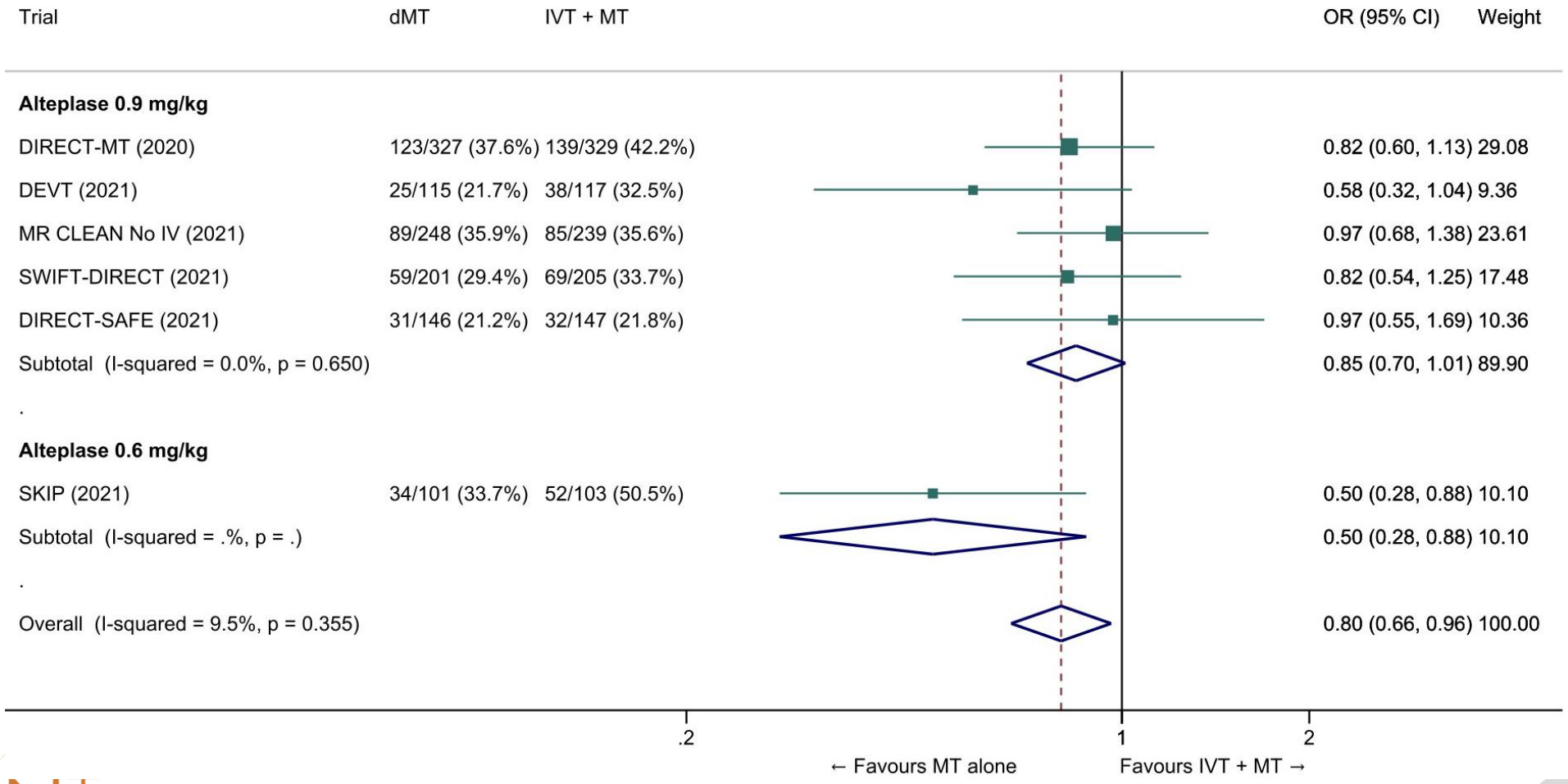
Direct MT vs. IVT plus MT

Any intracranial haemorrhage



Unadj. OR 0.80 (95% CI 0.66 to 0.96)

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Evidence-based Recommendation

Mothership, ≤4.5 hrs of symptom onset

For patients directly admitted to a thrombectomy-capable centre for an acute ischaemic stroke (≤4.5 hrs of symptom onset) with anterior circulation large vessel occlusion and who are eligible for both treatments, **we recommend intravenous thrombolysis plus mechanical thrombectomy** over mechanical thrombectomy alone.

Both treatments should be performed **as early as possible** after hospital arrival. Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis, and intravenous thrombolysis should not delay mechanical thrombectomy.

Quality of evidence: **Moderate** ⊕⊕⊕

Strength of recommendation: **Strong** ↑↑

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Expert Consensus Statement

Mothership, wake-up stroke

For patients directly admitted to a thrombectomy-capable centre within 4.5 hours of symptom recognition after wake-up stroke caused by anterior circulation large vessel occlusion, **we suggest intravenous thrombolysis plus mechanical thrombectomy** over mechanical thrombectomy alone **in selected patients**.

The selection criteria are detailed in the corresponding European Guidelines. Notably, eligibility imaging criteria for IVT include DWI-FLAIR mismatch or perfusion core/penumbra mismatch*.

*Perfusion core/penumbra mismatch:
- Infarct core** volume < 70 ml
- and Critically hypoperfused† volume / Infarct core** volume > 1.2
- and Mismatch volume > 10 ml

** rCBF <30% (CT perfusion) or ADC < 620 $\mu m^2/s$ (Diffusion MRI)
† Tmax >6s (perfusion CT or perfusion MRI)

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2021 ESO Guidelines on intravenous thrombolysis (Berge E et al, Eur J Stroke 6(1):I-LXII)

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PICO Question

Drip-and-ship, ≤4.5 hrs of symptom onset

PICO 2: For large vessel occlusion acute ischaemic stroke (≤ 4.5 hrs of symptom onset) patients **admitted to a non-thrombectomy capable centre** and eligible for both treatments, does mechanical thrombectomy alone compared with intravenous thrombolysis plus mechanical thrombectomy lead to:

a) a non-inferior proportion of patients with good outcome (mRS 0-2) at 90 days?
b) non-inferior or better results on other efficacy outcomes (whole range of the mRS; mRS 0-1; successful reperfusion)?
c) a reduction in the risk of adverse events (mortality at 90 days, intracranial haemorrhage)?

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Evidence-based Recommendation

Drip-and-ship, ≤4.5 hrs of symptom onset

For patients admitted to a non-thrombectomy-capable centre for an acute ischaemic stroke (≤4.5 hrs of symptom onset) with anterior circulation large vessel occlusion and who are eligible for both treatments, **we recommend intravenous thrombolysis followed by rapid transfer to a centre with thrombectomy facilities** over omitting intravenous thrombolysis and transfer to a centre with thrombectomy facilities.

Intravenous thrombolysis should not delay the transfer to a centre with thrombectomy facilities.

Quality of evidence: **Low** ⊕⊕

Strength of recommendation: **Strong** ↑↑

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Expert Consensus Statement

Drip-and-ship, wake-up stroke

For patients admitted to a non-thrombectomy capable centre within 4.5 hours of symptom recognition after wake-up stroke caused by anterior circulation large vessel occlusion, **we suggest intravenous thrombolysis plus mechanical thrombectomy** over mechanical thrombectomy alone **in selected patients**.

The selection criteria are detailed in the corresponding European Guidelines. Notably, eligibility imaging criteria for IVT include DWI-FLAIR mismatch or perfusion core/penumbra mismatch*.

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Discussion

Choice of the non-inferiority margin

- Is 1.3% too stringent?
- Only accepting a margin of 5.9% would lead to the conclusion of non-inferiority
  …is it really acceptable?

Historical trials	Intervention	Control	Unadj. 'risk' difference (mRS 0-2)	NNT
MR CLEAN	MT + Best medical therapy	Best medical therapy	13.5%	7
NINDS tPA trial	IVT	Placebo	11.9%	8
EXTEND	IVT	Placebo	6.7%	15
ECASS-3	IVT	Placebo	5.0%	20

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Conclusions

- Randomized trials only included:
  - Patients with anterior circulation large vessel occlusion strokes
  - Eligible for alteplase within 4.5hrs of symptom onset
  - Admitted to a thrombectomy-capable centre

- In that setting, non-inferiority of direct MT has not been demonstrated (1.3%, or even 5%)
- Therefore, in the absence of contraindication, **we recommend IVT before MT**
- **IVT should not delay MT or the transfer to a center with MT facilities**

- We also suggest IVT before MT in selected patients with wake-up stroke (expert opinion)

- These recommendations may be updated in case IPD meta-analyses disclose subgroups of ‘mothership’ patients in whom direct MT is superior to IVT + MT

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