

European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke

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Eur Stroke J: Vol 6, Issue 1, 2021

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Summary of recommendations

1 - European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke





This guideline is published in the European Stroke Journal.

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8.1 - Treatment within 4.5 h of onset



Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: High ++++

8.2 - Treatment between 4.5 and 9 h after known onset without use of advanced imaging



Strong recommendation against

For patients with acute ischaemic stroke of 4.5–9 h duration (known onset time), and with no brain imaging other than plain CT, we recommend no intravenous thrombolysis.

Quality of evidence: Moderate $\oplus \oplus \oplus$

8.3 - Treatment between 4.5 and 9 h after known onset with the use of advanced imaging



Strong recommendation

For patients with ischaemic stroke of 4.5–9 h duration (known onset time) and with CT or MRI core/ perfusion mismatch*, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

*In the individual participant data meta-analysis by Campbell et al.,[34] core/perfusion mismatch was assessed with an automated processing software and defined as follows:

- 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 µm2/s (Diffusion MRI)

[†]Tmax >6 s (perfusion CT or perfusion MRI)

For patients with no CT or MRI core/perfusion mismatch, please see the expert consensus statement below.



Consensus recommendation

Expert consensus statement

For patients with ischaemic stroke of 4.5–9 h duration (known onset), and with no CT or MRI core/ perfusion mismatch, 9 of 9 group members suggest against IVT with alteplase.



Consensus recommendation

Expert consensus statement

For patients presenting directly to a thrombectomy centre with ischaemic stroke of 4.5–9 h duration (known onset) with CT or MRI core/perfusion mismatch and who are eligible for mechanical thrombectomy, the group members could not reach a consensus regarding whether intravenous thrombolysis should be used before mechanical thrombectomy.

For patients presenting to a non-thrombectomy centre with ischaemic stroke of 4.5–9 h duration (known onset) with CT or MRI core/perfusion mismatch and who are eligible for mechanical thrombectomy, 6 of 9 group members suggest intravenous thrombolysis before mechanical thrombectomy.

8.4 - Stroke on awakening from sleep/unknown onset



Strong recommendation

For patients with acute ischaemic stroke on awakening from sleep, who were last seen well more than 4.5 h earlier, who have MRI DWI-FLAIR mismatch, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: High ⊕⊕⊕⊕



Strong recommendation

For patients with acute ischaemic stroke on awakening from sleep, who have CT or MRI core/perfusion mismatch* within 9 h from the midpoint of sleep, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate ⊕⊕⊕

*In the EOS individual participant data meta-analysis,[46] core/perfusion mismatch was assessed with an automated processing software and defined as follows:

- 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 mm2/s (Diffusion MRI)
- [†] Tmax >6 s (perfusion CT or perfusion MRI)



Consensus recommendation

Expert consensus statement

For patients presenting directly to a thrombectomy centre with acute ischaemic stroke on awakening from sleep, who would be eligible for both IVT and mechanical thrombectomy, 6 of 9 group members suggest IVT before MT.

For patients presenting to a non-thrombectomy centre with acute ischaemic stroke on awakening from sleep, who would be eligible for both IVT and mechanical thrombectomy, 7 of 9 group members suggest IVT before MT.

8.5 - Tenecteplase



Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration and not eligible for thrombectomy, we suggest intravenous thrombolysis with alteplase over intravenous thrombolysis with tenecteplase. Please see PICO 5.2 for patients eligible for mechanical thrombectomy.

Quality of evidence: Low ++



Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom intravenous thrombolysis is considered before thrombectomy, we suggest intravenous thrombolysis with tenecteplase 0.25 mg/kg over intravenous thrombolysis with alteplase 0.9 mg/kg.

Quality of evidence: Low ++

8.6 - Alternative doses



Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration who are eligible for intravenous thrombolysis, we recommend standard-dose alteplase (0.9 mg/kg) over low-dose alteplase.

Quality of evidence: High ⊕⊕⊕⊕

8.7 - Adjunctive therapies (i.e. antithrombotic agents, ultrasound)

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, we recommend no antithrombotic drugs within 24 h of intravenous thrombolysis over antithrombotic drugs as an adjunct therapy to intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, we recommend against ultrasound augmentation in patients receiving intravenous thrombolysis.

Quality of evidence: Low $\oplus \oplus$

8.8 - Higher age, multimorbidity, frailty or prior disability



Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, who are over 80 years of age, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: High ⊕⊕⊕⊕



Consensus recommendation

Expert consensus statement

Nine of nine group members believe that age alone should not be a limiting factor for IVT, even in other situations covered in the present guidelines (e.g. wake-up stroke; ischaemic stroke of 4.5–9 h duration (known onset time) with CT or MRI core/perfusion mismatch; minor stroke with disabling symptoms).



Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with multimorbidity, frailty or prestroke disability, we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Very low \oplus

8.9 - Minor stroke and stroke with rapidly improving neurological signs



Strong recommendation

For patients with acute minor, disabling ischaemic stroke of <4.5 h duration, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate ⊕⊕⊕



Weak recommendation against

For patients with acute minor non-disabling ischaemic stroke of <4.5 h duration, we suggest no intravenous thrombolysis. For patients with minor stroke and large-vessel occlusion, please refer to the section below (PICO 9.3).

Quality of evidence: Moderate ⊕⊕⊕

For patients with acute minor non-disabling ischaemic stroke of <4.5 h duration, and with proven large-vessel occlusion, there is insufficient evidence to make an evidence-based recommendation. Please see the Expert consensus statement below.
Quality of evidence: Very low ⊕
Consensus recommendation
Expert consensus statement
For patients with acute minor, non-disabling ischaemic stroke of <4.5 h duration, and with large-vessel occlusion, 6 of 8 group members suggest intravenous thrombolysis with alteplase.
For patients with acute ischaemic stroke of <4.5 h duration, and rapidly improving neurological signs, which are still disabling, there is insufficient evidence to make a recommendation. Please see the Expert consensus statement below.
Quality of evidence: Very low ⊕
Consensus recommendation
Expert consensus statement
For patients with acute ischaemic stroke of <4.5 h duration, and rapidly improving neurological signs, which are still

8.10 - Severe stroke

Strong recommendation

symptoms.

For patients with clinically severe acute ischaemic stroke of <4.5 h duration, we recommend intravenous thrombolysis with alteplase.

disabling, 8 of 9 group members suggest intravenous thrombolysis with alteplase. The group agreed that the treatment decision should be based on the clinical status at presentation, and that it is not justifiable to wait for resolution of

Quality of evidence: Moderate ⊕⊕⊕

Weak recommendation

For patients with acute ischaemic stroke of < 4.5 h duration, and with severe stroke, defined by the extent of early ischaemic changes on CT, we suggest that intravenous thrombolysis with alteplase be considered in selected cases (see the Expert consensus statement below).

Quality of evidence: Very Low



Consensus recommendation

Expert consensus statement

Seven of nine group members voted for intravenous thrombolysis with alteplase in selected patients with severe stroke associated with extended radiological signs of infarction (e.g., early ischemic change of more than 1/3 of the middle cerebral artery territory or ASPECTS <7 on plain CT). Patient selection criteria might include eligibility for an alternative reperfusion strategy (mechanical thrombectomy), results of advanced imaging (notably core/perfusion mismatch), time since symptom onset, extent of white matter lesions, other contraindications for IVT, and pre-stroke disability.

8.11 - High blood pressure and high blood glucose level



Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, and with persistently increased systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg even after blood pressure lowering treatment, we suggest no intravenous thrombolysis.

Quality of evidence: Very low



Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg, which has subsequently been lowered to <185 and <110 mmHg, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Low ++



Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with known pre-stroke hypertension, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate ⊕⊕⊕



Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with blood glucose levels above 22.2 mmol/L (400 mg/dL), we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Very Low

Intravenous thrombolysis should not prevent the administration of insulin therapy in acute ischaemic stroke patients with high blood glucose levels.[144]



Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with known diabetes mellitus, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate ⊕⊕⊕

8.12 - Use of antithrombotic drugs before the stroke

Strong recommendation For patients with acute ischaemic stroke of <4.5 h duration, who used single or dual antiplatelet agents prior to the stroke, we suggest intravenous thrombolysis with alteplase. Quality of evidence: Low ++ Strong recommendation For patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists and have INR ≤1.7 we recommend intravenous thrombolysis with alteplase. Quality of evidence: Low $\oplus \oplus$ Strong recommendation against For patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists and have INR >1.7 we recommend no intravenous thrombolysis. Quality of evidence: Very Low Strong recommendation against For patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists, and for whom the results of coagulation testing is unknown, we recommend no intravenous thrombolysis. Quality of evidence: Very low Strong recommendation against For patients with acute ischaemic stroke of <4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and for whom there is no specific coagulation tests available (i.e. calibrated anti-Xa-activity for factor Xa inhibitors, thrombin time for dabigatran, or the NOAC blood concentrations), we suggest no intravenous thrombolysis. Quality of evidence: Very Low For patients with acute ischaemic stroke of <4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and who have an anti-Xa activity <0.5 U/ml (for factor Xa inhibitors) or thrombin time <60 s (for direct thrombin inhibitors), there is insufficient evidence to make an evidence-based recommendation. Please see the Expert consensus statement below. Quality of evidence: Very low For patients with acute ischaemic stroke of <4.5 h duration, who used dabigatran during the last 48 h before stroke onset, there is insufficient evidence to make a recommendation for or against the use of the combination of idarucizumab and intravenous thrombolysis with alteplase over no intravenous thrombolysis. Please see the Expert consensus statement below. Quality of evidence: Very low



Consensus recommendation

Expert consensus statement

For patients with acute ischaemic stroke of <4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and who have an anti-Xa activity <0.5U/ml (for factor Xa inhibitors) or thrombin time <60 s (for direct thrombin inhibitors) 7 of 9 group members suggest IVT with alteplase.

For patients with acute ischaemic stroke of <4.5 h duration, who used dabigatran during the last 48 h before stroke onset, 8 of 9 group members suggest the combination of idarucizumab and intravenous thrombolysis with alteplase over no intravenous thrombolysis.

For patients with acute ischaemic stroke of <4.5 h duration, who used factor Xa inhibitors during the last 48 h before stroke onset, 9 of 9 group members suggest against the combination of andexanet and intravenous thrombolysis with alteplase over no intravenous thrombolysis.

8.13 - Potential risk factors for bleeding



Weak recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, and with known platelet count $<100\times10^9$ /L, we suggest no intravenous thrombolysis.

Quality of evidence: Very low



Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with unknown platelet count before initiation of intravenous thrombolysis and no reason to expect abnormal values, we recommend starting intravenous thrombolysis with alteplase while waiting for lab tests results.

Quality of evidence: Very low



Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration and with major surgery on a non-compressible site where bleeding is likely to lead to significant haemorrhage (e.g., abdomen, chest, skull, well-vascularized tissues, or large artery) during the preceding 14 days, we recommend no intravenous thrombolysis.

Quality of evidence: Very low



For patients with acute ischaemic stroke of <4.5 h duration, and a history of intracranial haemorrhage, there is insufficient evidence to make an evidence-based recommendation. Please see the Expert consensus statement below.

Quality of evidence: Very low



Consensus recommendation

Expert consensus statement

For patients with acute ischaemic stroke of <4.5 h duration and with a history of intracranial haemorrhage, 8 of 9 members suggest intravenous thrombolysis with alteplase in selected cases. For example, intravenous thrombolysis may be considered if a long time has elapsed since the haemorrhage, or if there was a non-recurrent or treated underlying cause for the haemorrhage (e.g. trauma, subarachnoid haemorrhage with subsequent endovascular or surgical aneurysm removal, or use of specific antithrombotic medication).

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration, for whom cerebral microbleed burden is unknown or known to be low (e.g. <10), we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

Weak recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, for whom cerebral microbleed burden has been previously reported to be high (e.g. >10), we suggest no intravenous thrombolysis.

Quality of evidence: Low ++

Consensus recommendation

Expert consensus statement

For patients with acute ischaemic stroke within 4.5 h of stroke onset, 9 of 9 members suggest against systematic screening with MRI to assess cerebral microbleed burden before making a treatment decision regarding intravenous thrombolysis.

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and small to moderate burden of white matter lesions, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate ⊕⊕⊕

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and high burden of white matter lesions, we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration, who have an unruptured cerebral artery aneurysm, we suggest IVT with alteplase.

Quality of evidence: Very low \oplus

8.14 - Other co-existing conditions

For patients with acute ischaemic stroke of <4.5 h duration, and with a history of ischaemic stroke during the last three months, there is insufficient evidence to make an evidence-based recommendation recommendation. Please see the Expert consensus statement below.

Quality of evidence: Very low \oplus

Consensus recommendation **Expert consensus statement** For patients with acute ischaemic stroke of <4.5 h duration, and a history of ischemic stroke within the last three months, nine of nine members voted for intravenous thrombolysis with alteplase in selected cases, for example in case of a small infarct, stroke occurring more than one month earlier, or good clinical recovery. Weak recommendation For patients with acute ischaemic stroke of <4.5 h duration who have seizures at time of stroke onset, and for whom there is no suspicion of a stroke mimic or significant head trauma, we suggest intravenous thrombolysis with alteplase. Quality of evidence: Very low Strong recommendation against For patients with acute ischaemic stroke of <4.5 h duration and with aortic arch dissection we recommend no intravenous thrombolysis. Quality of evidence: Very low Weak recommendation For patients with acute ischaemic stroke of <4.5 h duration and with isolated cervical artery dissections, we suggest intravenous thrombolysis with alteplase. Quality of evidence: Low ++ For patients with acute ischaemic stroke of < 4.5 h duration and with intracerebral artery dissections, there is insufficient evidence to make a recommendation. Please see the Expert consensus statement below. Quality of evidence: Very low Consensus recommendation For patients with acute ischaemic stroke of <4.5 h duration and with an intracerebral artery dissection, 6 of 9 group members suggest against intravenous thrombolysis with alteplase. Weak recommendation against For patients with acute ischaemic stroke of <4.5 h duration and with history of subacute (>6 h) ST-elevation myocardial infarction during the last seven days, we suggest no IVT. Quality of evidence: Very low

For patients with acute ischaemic stroke of <4.5 h duration and with history of ST-elevation myocardial infarction of more than a week to three months, there is insufficient evidence to make a recommendation. Please see the Expert

consensus statement below.

Quality of evidence: Very low

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration and with a history of non-ST-elevation myocardial infarction during the last three months, we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Very low

Consensus recommendation

Expert consensus statement

For patients with acute ischaemic stroke of <4.5 h duration and with history of ST-elevation myocardial infarction of more than a week to three months, nine of nine group members suggest IVT with alteplase in specific situations. Variables

to take into account are the size of the myocardial infarction, whether recanalisation therapy was given for the myocardial infarction, and echocardiographic findings.



Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration and with a clear or suspected diagnosis of infective endocarditis, we suggest no intravenous thrombolysis.

Quality of evidence: Low ++

9 - Discussion

10 - Disclaimers

10.1 - Declaration of conflicting interests

10.2 - Funding

10.3 - Ethical approval

10.4 - Informed consent

10.5 - Guarantor

10.6 - Contributorship

10.7 - Acknowledgments

11 - Supplemental material

12 - References

1 - European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke

This guideline is published in the European Stroke Journal.

New

2 - Authors

In memory of Professor Eivind Berge



This guideline was co-chaired and led by Professor Eivind Berge, Consultant Cardiologist at the Department of Internal Medicine at Oslo University Hospital. The ESO IVT guideline module working group deeply felt the loss of his calm leadership, thoughtfulness, and thoroughness after his death. Any mistakes or omissions are ours alone.

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3 - Abstract

Intravenous thrombolysis is the only approved systemic reperfusion treatment for patients with acute ischaemic stroke. These European Stroke Organisation (ESO) guidelines provide evidence-based recommendations to assist physicians in their clinical decisions with regard to intravenous thrombolysis for acute ischaemic stroke. These guidelines were developed based on the ESO standard operating procedure and followed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. The working group identified relevant clinical questions, performed systematic reviews and meta-analyses of the literature, assessed the quality of the available evidence, and wrote recommendations. Expert consensus statements were provided if not enough evidence was available to provide recommendations based on the GRADE approach. We found high quality evidence to recommend intravenous thrombolysis with alteplase to improve functional outcome in patients with acute ischemic stroke within 4.5 h after symptom onset. We also found high quality evidence to recommend intravenous thrombolysis with alteplase in patients with acute ischaemic stroke on awakening from sleep, who were last seen well more than 4.5 h earlier, who have MRI DWI-FLAIR mismatch, and for whom mechanical thrombectomy is not planned. These guidelines provide further recommendations regarding patient subgroups, late time windows, imaging selection strategies, relative and absolute contraindications to alteplase, and tenecteplase. Intravenous thrombolysis remains a cornerstone of acute stroke management. Appropriate patient selection and timely treatment are crucial. Further randomized controlled clinical trials are needed to inform clinical decision-making with regard to tenecteplase and the use of intravenous thrombolysis before mechanical thrombectomy in patients with large vessel occlusion.

4 - Summary table of recommendations

Table 12. Summary of PICO questions, evidence based recommendations, and expert consensus statements.

Topic/PICO Question Recommendations Expert consensus statement 0-4.5 h time window I.I: In patients with acute For patients with acute ischaemic stroke of ischaemic stroke of <4.5 h < 4.5 h duration, we recommend intraduration, does intravenous venous thrombolysis with alteplase. thrombolysis with alteplase Quality of evidence: High + lead to better functional out-Strength of recommendation: Strong † † come than no intravenous thrombolysis?

4.5-9h time window (known onset), plain CT

2.1: In patients with acute ischaemic stroke of 4.5–9 h duration (known onset time) selected with plain CT, does intravenous thrombolysis with alteplase lead to better functional outcome than no intravenous thrombolysis? For patients with acute ischaemic stroke of 4.5–9 h duration (known onset time), and with no brain imaging other than plain CT, we recommend no intravenous thrombolysis.

Quality of evidence: Moderate + Strength of recommendation: Strong | |

4.5-9h time window (known onset), perfusion mismatch

3.1: In patients with ischaemic stroke of 4.5–9 h duration (known onset time), and with CT or MRI core/perfusion mismatch, does intravenous thrombolysis with alteplase lead to better functional outcome than no intravenous thrombolysis?

For patients with ischaemic stroke of 4.5— 9 h duration (known onset time) and with CT or MRI core/perfusion mismatch*, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Low $\oplus \oplus$ Strength of recommendation: Strong $\uparrow \uparrow$

- *In the individual participant data metaanalysis by Campbell et al., 34 core/perfusion mismatch was assessed with an automated processing software and defined as follows:
- 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 µm2/s (Diffusion MRI)
- † Tmax >6s (perfusion CT or perfusion MRI)

For patients with ischaemic stroke of 4.5-9 h duration (known onset), and with no CT or MRI core/perfusion mismatch, 9 of 9 group members suggest against IVT with alteplase.

For patients presenting directly to a thrombectomy centre with ischaemic stroke of 4.5–9 h duration (known onset) with CT or MRI core/ perfusion mismatch and who are eligible for mechanical thrombectomy, the group members could not reach a consensus regarding whether intravenous thrombolysis should be used before mechanical thrombectomy.

For patients presenting to a nonthrombectomy centre with ischaemic stroke of 4.5–9 h duration (known onset) with CT or MRI core/perfusion mismatch and who are eligible for mechanical thrombectomy, 6/9 group members suggest intravenous thrombolysis before mechanical thrombectomy.

Wake-up stroke/Unknown onset

4.1: In patients with acute ischaemic stroke on awakening from sleep / unknown onset, does intravenous thrombolysis For patients with acute ischaemic stroke on awakening from sleep, who were last seen well more than 4.5 h earlier, who have MRI DWI-FLAIR mismatch, and for For patients presenting directly to a thrombectomy centre with acute ischaemic stroke on awakening from sleep, who would be eligible for both

Topic/PICO Question

with alteplase lead to better functional outcome than no intravenous thrombolysis?

Recommendations

whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: High $\oplus \oplus \oplus \oplus$ Strength of recommendation: Strong ††

For patients with acute ischaemic stroke on awakening from sleep, who have CT or MRI core/perfusion mismatch* within nine hours from the midpoint of sleep, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate $\oplus \oplus \oplus$ Strength of recommendation: Strong ††

- *In the EOS individual participant data meta-analysis, 46 core/perfusion mismatch was assessed with an automated processing software and defined as follows:
- 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 µm2/s (Diffusion MRI)
- † Tmax >6s (perfusion CT or perfusion MRI)

Expert consensus statement

IVT and mechanical thrombectomy, 6/9 group members suggest IVT before MT.

For patients presenting to a nonthrombectomy centre with acute ischaemic stroke on awakening from sleep, who would be eligible for both IVT and mechanical thrombectomy, 7/9 group members suggest IVT before MT.

Tenecteplase - no large vessel occlusion

5.1: In patients with acute ischaemic stroke of <4.5 h duration, does IVT with tenecteplase lead to better functional outcome than IVT with alteplase? For patients with acute ischaemic stroke of <4.5 h duration and not eligible for thrombectomy, we suggest intravenous thrombolysis with alteplase over intravenous thrombolysis with tenecteplase. Please see paragraph 5.2 for patients eligible for mechanical thrombectomy.

Quality of evidence: Low ⊕⊕ Strength of recommendation: Weak ↑?

Tenecteplase - large vessel occlusion

5.2: In patients with acute ischaemic stroke of <4.5 h duration and with large vessel occlusion, who are candidates for mechanical thrombectomy, and for whom intravenous thrombolysis is considered before thrombectomy, does IVT with tenecteplase lead to better functional</p>

For patients with acute ischaemic stroke of < 4.5 h duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom intravenous thrombolysis is considered before thrombectomy, we suggest intravenous thrombolysis with tenecteplase 0.25 mg/kg over intravenous thrombolysis with alteplase 0.9 mg/kg.

Topic/PICO Question	Recommendations	Expert consensus statement
outcome than IVT with alteplase?	Quality of evidence: Low ⊕⊕ Strength of recommendation: Weak †?	
Low-dose alteplase		
6.1: In patients with acute ischaemic stroke of <4.5 h duration, does intravenous thrombolysis with low-dose alteplase lead to non-inferior (not worse) functional out- come compared to standard- dose alteplase?	For patients with acute ischaemic stroke of <4.5 h duration who are eligible for intravenous thrombolysis, we recommend standard-dose alteplase (0.9 mg/kg) over low-dose alteplase. Quality of evidence: High + ++++ Strength of recommendation: Strong ↑↑	
Adjunct antithrombotic therapy		
7.1: In patients with acute ischaemic stroke of <4.5 h duration, does antithrombotic agents in addition to IVT lead to better functional outcome than IVT alone?	For patients with acute ischaemic stroke of <4.5 h duration, we recommend no antithrombotic drugs within 24 h of intravenous thrombolysis over antithrombotic drugs as an adjunct therapy to intravenous thrombolysis with alteplase. Quality of evidence: Low Strength of recommendation: Strong	
Sonothrombolysis		
7.2: In patients with acute	For patients with acute ischaemic stroke of	
ischaemic stroke of <4.5 h duration, does ultrasound augmentation of IVT lead to	< 4.5 h duration, we recommend against ultrasound augmentation in patients receiving intravenous thrombolysis.	
hamas for advantage a	One line of wilder on Long (D/D)	

Higher age, multimorbidity, prior disability

8.1: In patients with acute ischaemic stroke of <4.5 h duration, who are over 80 years of age, does intravenous thrombolysis with alteplase lead to better functional outcome than no IVT?

better functional outcome

than IVT alone?

- 8.2: In patients with acute ischaemic stroke of <4.5 h duration, who have multimorbidity, frailty, or prior disability, does intravenous thrombolysis with alteplase lead to better functional outcome than no IVT?
- For patients with acute ischaemic stroke of <4.5 h duration, who are over 80 years of age, we recommend intravenous thrombolysis with alteplase.

Strength of recommendation: Strong | |

Quality of evidence: Low ++

- Quality of evidence: **High** $\oplus \oplus \oplus \oplus$ Strength of recommendation: **Strong** $\uparrow \uparrow$
- For patients with acute ischaemic stroke of <4.5 h duration, and with multimorbidity, frailty or pre-stroke disability, we suggest intravenous thrombolysis with alteplase.
- Quality of evidence: Very low \oplus Strength of recommendation: Weak \uparrow ?
- 9/9 group members believe that age alone should not be a limiting factor for IVT, even in other situations covered in the present guidelines (e.g. wake-up stroke; ischaemic stroke of 4.5–9 h duration (known onset time) with CT or MRI core/ perfusion mismatch; minor stroke with disabling symptoms).

Topic/PICO Question	Recommendations	Expert consensus statement
Minor stroke (disabling) 9.1: In patients with acute minor, disabling ischaemic stroke of <4.5 h duration, does IVT with alteplase lead to better func- tional outcome than no IVT?	For patients with acute minor, disabling ischaemic stroke of < 4.5 h duration, we recommend intravenous thrombolysis with alteplase. Quality of evidence: Moderate \$\therefore\	
Minor stroke (non-disabling) 9.2: In patients with acute minor, non-disabling ischaemic stroke of <4.5 h duration, does IVT with alteplase lead to better functional outcome than no IVT?	For patients with acute minor non-disabling ischaemic stroke of <4.5 h duration, we suggest no intravenous thrombolysis. For patients with minor stroke and large-vessel occlusion, please refer to the section below (PICO 9.3). Quality of evidence: Moderate ++++ Strength of recommendation: Weak 1?	
9.3: In patients with acute minor, non-disabling ischaemic stroke of <4.5 h duration, and with proven large vessel occlusion, does IVT with alteplase lead to better functional outcome than no IVT?	Strength of recommendation. Yveak 1:	For patients with acute minor, non- disabling ischaemic stroke of <4.5 h duration, and with large-vessel occlusion, 6 of 8 group members suggest intravenous thrombolysis with alteplase.
Rapidly improving symptoms 9.4: In patients with acute ischaemic stroke of <4.5 h duration, and with rapidly improving neurological signs, does IVT with alteplase lead to better functional outcome than no IVT?		For patients with acute ischaemic stroke with < 4.5 h duration, and rapidly improving neurological signs, which are still disabling, 8 of 9 group members suggest intravenous thrombolysis with alteplase. The group agreed that the treatment decision should be based on the clinical status at presentation, and that it is not justifiable to wait for resolution of symptoms.
Severe stroke 10.1: In patients with severe acute ischaemic stroke of <4.5 h duration, does IVT with alteplase lead to better func- tional outcome than no IVT?	For patients with clinically severe acute ischaemic stroke of < 4.5 h duration, we recommend intravenous thrombolysis with alteplase. Quality of evidence: Moderate ++++ Strength of recommendation: Strong ↑↑ For patients with acute ischaemic stroke of < 4.5 h duration, and with severe stroke, defined by the extent of early ischaemic changes on CT, we suggest that intravenous thrombolysis with alteplase be considered in selected cases (see the	7 of 9 group members voted for intra- venous thrombolysis with alteplase in selected patients with severe stroke associated with extended radiologi- cal signs of infarction (e.g., early ischemic change of more than 1/3 of the middle cerebral artery territory or ASPECTS <7 on plain CT). Patient selection criteria might include eligibility for an alternative reperfusion strategy (mechanical thrombectomy), results of advanced imaging (notably perfusion/core

Topic/PICO Question	Recommendations	Expert consensus statement
	Expert consensus statement).	mismatch), time since symptom
	Quality of evidence: Very Low ⊕	onset, and pre-stroke disability.
	Strength of recommendation: Weak †?	
High Blood pressure on admission	on	
II.I: In patients with acute	For patients with acute ischaemic stroke of	
ischaemic stroke of <4.5 h	< 4.5 h duration, and with persistently	
duration, and with persistently	increased systolic blood pressure	
increased blood pressure	>185 mmHg or diastolic blood pressure	
above 185/110 mmHg, even	>110 mm Hg even after blood pressure	
after blood pressure lowering	lowering treatment, we suggest no	
treatment, does IVT with	intravenous thrombolysis.	
alteplase lead to better func-	Quality of evidence: Very low \oplus	
tional outcome than no IVT?	Strength of recommendation: Strong 1	
II.2: In patients with acute	For patients with acute ischaemic stroke of	
ischaemic stroke of <4.5 h	<4.5 h duration, and with systolic blood	
duration, and with increased	pressure > 185 mm Hg or diastolic	
blood pressure above 185/	blood pressure > 110 mm Hg, which has	
I 10 mm Hg, which has subse-	subsequently been lowered to <185 and	
quently been lowered to	<110 mm Hg, we recommend intrave-	
below 185/110 mm Hg, does	nous thrombolysis with alteplase.	
IVT with alteplase lead to better functional outcome	Quality of evidence: Low $\oplus \oplus$ Strength of recommendation: Strong ††	
than no IVT?	Strength of recommendation, salong	
Pre-stroke hypertension		
II.3: In patients with acute	For patients with acute ischaemic stroke of	
ischaemic stroke of <4.5 h	<4.5 h duration, and with known pre-	
duration, and with known pre- stroke hypertension, does IVT	stroke hypertension, we recommend intravenous thrombolysis with alteplase.	
with alteplase lead to better	Quality of evidence: Moderate	
functional outcome than no	Strength of recommendation: Strong ↑↑	
IVT?	Shedger or recommendation out one [1]	
High glucose level on admission		
11.4: In patients with acute	For patients with acute ischaemic stroke of	
ischaemic stroke of <4.5 h	<4.5 h duration, and with blood glucose	
duration, and with blood glu-	levels above >22.2 mm ol/L (400 mg/dL),	
cose level above 22.2 mmol/L	we suggest intravenous thrombolysis	
(>400 mg/dL), does IVT with	with alteplase.	
alteplase lead to better func-	Quality of evidence: Very Low ⊕	
tional outcome than no IVT?	Strength of recommendation: Weak †?	
	Intravenous thrombolysis should not pre- vent the administration of insulin thera-	
	py in acute ischaemic stroke patients	
	with high blood glucose levels. 144	
Diabetes mellitus		
I I.5: In patients with acute	For patients with acute ischaemic stroke of	
ischaemic stroke of <4.5 h	<4.5 h duration, and with known diabe-	
duration and with known	ter mallitur use recommend interveness	

tes mellitus, we recommend intravenous

duration, and with known

Topic/PICO Question

Recommendations

Expert consensus statement

diabetes mellitus, does IVT with alteplase lead to better functional outcome than no IVT?

Antiplatelet agents prior to stroke

12.1: In patients with acute ischaemic stroke of <4.5 h duration, who use antiplatelet agents, does IVT with alteplase lead to better functional outcome than no IVT? For patients with acute ischaemic stroke of <4.5 h duration, who used single or dual antiplatelet agents prior to the stroke, we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Low $\oplus \oplus$ Strength of recommendation: Strong $\uparrow \uparrow$

Anticoagulants before stroke (VKA)

12.2: In patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists, does IVT with alteplase lead to better functional outcome than no IVT? For patients with acute ischaemic stroke of $<4.5 \, h$ duration, who use vitamin K antagonists and have INR \le I.7 we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Low $\oplus \oplus$ Strength of recommendation: Strong $\uparrow \uparrow$

For patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists and have INR >1.7 we recommend no intravenous thrombolysis.

Quality of evidence: Very Low \oplus Strength of recommendation: Strong $\downarrow\downarrow$

For patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists, and for whom the results of coagulation testing is unknown, we recommend no intravenous thrombolysis.

Quality of evidence: Very low \oplus Strength of recommendation: Strong $\downarrow\downarrow$

Anticoagulants before stroke (NOACs)

12.3: In patients with acute ischaemic stroke of <4.5 h duration, who use NOACs, does IVT with alteplase lead to better functional outcome than no IVT? For patients with acute ischaemic stroke of <4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and for whom there is no specific coagulation tests available (i.e. calibrated anti-Xa-activity for factor Xa inhibitors, thrombin time for dabigatran, or the NOAC blood concentrations), we suggest no intravenous thrombolysis.

Quality of evidence: Very Low \oplus Strength of recommendation: Strong $\downarrow\downarrow$ For patients with acute ischaemic stroke of <4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and who have an anti-Xa activity <0.5 U/ml (for factor Xa inhibitors) or thrombin time <60 s (for direct thrombin inhibitors) 7 of 9 group members suggest IVT with alteplase.

For patients with acute ischaemic stroke of <4.5 h duration, who used dabigatran during the last 48 h before

Topic/PICO Question Recommendations Expert consensus statement stroke onset, 8/9 group members surgest the combination of idenuci-

stroke onset, 8/9 group members suggest the combination of idarucizumab and intravenous thrombolysis with alteplase over no intravenous thrombolysis.

For patients with acute ischaemic stroke of <4.5 h duration, who used factor Xa inhibitors during the last 48 h before stroke onset, 9/9 group members suggest against the combination of andexanet and intravenous thrombolysis with alteplase over no intravenous thrombolysis.

Low platelet count

13.1: In patients with acute ischaemic stroke of <4.5 h duration, who have low platelet count, does IVT with alteplase lead to better functional outcome than no IVT? For patients with acute ischaemic stroke of $<4.5\,h$ duration, and with known platelet count $<100\times10^9/L$, we suggest no intravenous thrombolysis.

Quality of evidence: Very low \oplus Strength of recommendation: Weak \bot ?

For patients with acute ischaemic stroke of <4.5 h duration, and with unknown platelet count before initiation of intravenous thrombolysis and no reason to expect abnormal values, we recommend starting intravenous thrombolysis with alteplase while waiting for lab tests results.

Quality of evidence: Very low \oplus Strength of recommendation: Strong $\uparrow \uparrow$

Recent trauma or surgery

13.2: In patients with acute ischaemic stroke of <4.5 h duration, who have a history of recent trauma, surgery or biopsy, does IVT with alteplase lead to better functional outcome than no IVT?

For patients with acute ischaemic stroke of <4.5 h duration and with major surgery on a non-compressible site where bleeding is likely to lead to significant haemorrhage (e.g., abdomen, chest, skull, well-vascularized tissues, or large artery) during the preceding 14 days, we recommend no intravenous thrombolysis.

Quality of evidence: Very low \oplus Strength of recommendation: Strong $\downarrow\downarrow$

History of intracranial hemorrhage

13.3: In patients with acute ischaemic stroke of < 4.5 h duration, who have a history of intracranial haemorrhage, For patients with acute ischaemic stroke of <4.5 h duration and with a history of intracranial haemorrhage, 8/9 members suggest intravenous

Topic/PICO Question Recommendations Expert consensus statement does IVT with alteplase lead to thrombolysis with alteplase in better functional outcome selected cases. For example, intrathan no IVT? venous thrombolysis may be considered if a long time has elapsed since the haemorrhage, if there was a specific underlying cause for the haemorrhage (e.g. trauma, subarachnoid haemorrhage with subsequent endovascular or surgical aneurysm removal, or use of specific antithrombotic medication). Microbleeds 13.4: In patients with acute For patients with acute ischaemic stroke of For patients with acute ischaemic stroke within 4.5 h of stroke onset, 9 ischaemic stroke of <4.5 h <4.5 h duration, for whom cerebral duration, who have cerebral microbleed burden is unknown or of 9 members suggest against screening with MRI to assess ceremicrobleeds, does NT with known to be low (e.g. <10), we suggest alteplase lead to better funcintravenous thrombolysis with alteplase. bral microbleed burden before Quality of evidence: Low ++ making a treatment decision regardtional outcome than no IVT? Strength of recommendation: Weak †? ing intravenous thrombolysis. For patients with acute ischaemic stroke of <4.5 h duration, for whom cerebral microbleed burden has been previously reported to be high (e.g. >10), we suggest no intravenous thrombolysis. Quality of evidence: Low ++ Strength of recommendation: Weak 1? White matter lesions 13.5: In patients with acute For patients with acute ischaemic stroke of ischaemic stroke of <4.5 h < 4.5 h duration, and small to moderate duration, who have cerebral burden of white matter lesions, we white matter lesions, does IVT recommend intravenous thrombolysis with alteplase lead to better with alteplase. functional outcome than no Quality of evidence: Moderate ++++ IVT? Strength of recommendation: Strong † † For patients with acute ischaemic stroke of <4.5 h duration, and high burden of white matter lesions, we suggest intravenous thrombolysis with alteolase. Quality of evidence: Low ++ Strength of recommendation: Weak †? Cerebral aneurysm 13.6: In patients with acute For patients with acute ischaemic stroke of ischaemic stroke of <4.5 h <4.5 h duration, who have an unrupduration, who have an unruptured cerebral artery aneurysm, we

suggest IVT with alteplase.

Quality of evidence: Very low \oplus Strength of recommendation: Weak †?

tured cerebral aneurysm, does

IVT with alteplase lead to

Topic/PICO Question	Recommendations	Expert consensus statement
better functional outcome than no IVT?		
History of ischaemic stroke 14.1: In patients with acute ischaemic stroke of <4.5 h duration, who have a history of ischaemic stroke during the last three months, does IVT with alteplase lead to better functional outcome than no IVT?		For patients with acute ischaemic stroke of <4.5 h duration, and a his tory of ischemic stroke within the last three months, nine of nine members voted for intravenous thrombolysis with alteplase in selected cases, for example in case of a small infarct, stroke occurring more than one month earlier, or good clinical recovery.
Seizure 14.2: In patients with acute ischaemic stroke of <4.5 h duration, who had a seizure at time of stroke onset, does IVT with alteplase lead to better functional outcome than no IVT?	For patients with acute ischaemic stroke of <4.5 h duration who have seizures at time of stroke onset, and for whom there is no suspicion of a stroke mimic or significant head trauma, we suggest intravenous thrombolysis with alteplase. Quality of evidence: Very low Strength of recommendation: Weak 1?	
Dissection		
I4.3: In patients with acute ischaemic stroke of <4.5 h duration, who have dissection in the aortic arch, in a carotid artery or in an intracerebral artery, does IVT with alteplase lead to better functional outcome than no IVT?	For patients with acute ischaemic stroke of <4.5 h duration and with acrtic arch dissection we recommend no intravenous thrombolysis. Quality of evidence: Very Iow Strength of recommendation: Strong For patients with acute ischaemic stroke of <4.5 h duration and with isolated cervical artery dissections, we suggest intravenous thrombolys is with alteplase. Quality of evidence: Low Strength of recommendation: Weak	For patients with acute ischaemic stroke of <4.5 h duration and with an intracerebral artery dissection, 6 9 group members suggest against intravenous thrombolysis with alteplase.
Myocardial infarction 14.4: In patients with acute ischaemic stroke of <4.5 h duration, who have had myocardial infarction during the last three months, does IVT with alteplase lead to better functional outcome than no IVT?	For patients with acute ischaemic stroke of <4.5 h duration and with history of subacute (>6 h) ST-elevation myocardial infarction during the last seven days, we suggest no IVT. Quality of evidence: Very Iow Strength of recommendation: Weak !? For patients with acute ischaemic stroke of <4.5 h duration and with a history of non-ST-elevation myocardial infarction during the last three months, we suggest intravenous thrombolys is with alteplase.	For patients with acute ischaemic stroke of <4.5 h duration and with history of ST-elevation myocardial infarction of more than a week to three months, 9/9 group members suggest IVT with alteplase in specific situations. Variables to take into account are the size of the myocardial infarction, whether recanalisation therapy was given for the myocardial infarction, and echocardiographic findings.
Topic/PICO Question	Recommendations	Expert consensus statement
	Quality of evidence: Very low ⊕ Strength of recommendation: Weak †?	
Infective endo carditis 14.5: In patients with acute ischaemic stroke of <4.5 h duration, who have infective endocarditis, does IVT with alteplase lead to better functional outcome than no IVT?	For patients with acute ischaemic stroke of <4.5 h duration and with a clear or suspected diagnosis of infective endocarditis, we suggest no intravenous thrombolysis. Quality of evidence: Low ### Strength of recommendation: Strong	

5 - Plain language summary

Patients with stroke due to blood clots in brain arteries ('ischaemic stroke') can be treated with clot-dissolving drugs called 'thrombolytics'. By dissolving blood clots, thrombolytic drugs improve brain blood supply and lead to better recovery. However, thrombolytic drugs may cause bleeding in the brain which can lead to worse disability or death. The most commonly used thrombolytic drug for ischemic stroke is called alteplase.

The guideline authors make recommendations about the use of thrombolytic drugs given into a vein for patients with acute ischaemic stroke. The guideline makes forty recommendations. The most important recommendations are:

- 1. To treat ischaemic stroke patients with alteplase if it can be started within 4.5 h of symptoms beginning. The stroke symptoms should be disabling at the time of treatment. The age of the patient does not matter.
- 2. Advanced brain imaging (magnetic resonance or CT perfusion) should be used to select patients for treatment with alteplase, if they present between 4.5 and 9 h after the start of symptoms, or if a stroke is noticed at waking from sleep.
- 3. To avoid treatment with low dose alteplase, or to add ultrasound or immediate antiplatelet drugs to alteplase because they do not give a better chance of surviving with no disability.
- 4. If an ischaemic stroke patient could be treated with alteplase, do not avoid treatment if the patient:
- has a diagnosis of high blood pressure, diabetes, previous stroke, or a heart attack
- takes antiplatelet drugs like aspirin
- At the time of stroke has a high blood glucose level, or an epileptic seizure (if the diagnosis of stroke is certain) or dissection of the carotid artery
- Has had a brain scan that shows a brain aneurysm that has not burst, or<10 tiny brain bleeds (microbleeds), or damage to the brain 'white matter'
- has had a brain bleed because of a cause unlikely to re-occur
- 5. Generally, to avoid treatment with alteplase if the ischaemic patient is taking blood thinning drugs such as a 'direct oral anticoagulants' or warfarin, unless:
- The patient is taking warfarin and the INR (a measure of blood clotting) is known to be<1.7.
- The patient had been prescribed a 'direct oral anticoagulant' (such as apixaban, dabigatran, rivaroxaban, edoxaban) but has not taken the drug in the 48 h before stroke.
- 6. Generally to avoid treatment with alteplase if the patient has recently had major surgery, major trauma, infection of the heart valves (endocarditis), or dissection of the aorta. If the patient is known to have more than ten tiny bleeds of the brain (microbleeds) or very low levels of blood platelets, treatment should be avoided, but looking for these with blood tests or extra brain scans should not delay treatment.
- 7. An alternative thrombolytic drug, tenecteplase, may be favored over alteplase before clot pulling treatment (thrombectomy), but its place to treat all patients is uncertain.
- 8. Once blood pressure is lower than 185 mmHg systolic or 110 mmHg diastolic, alteplase can be given safely.

The major recommendations were supported by high to moderate quality evidence. Other than for age and stroke severity, there was weaker evidence to support when to use alteplase in very particular situations.

6 - Introduction

Intravenous thrombolysis (IVT) with alteplase is the only approved systemic reperfusion treatment for patients with acute ischaemic stroke.[1] The drive to reduce times to IVT has led to more rapid treatment for stroke patients in some areas of Europe. It has blazed the trail for early stroke unit care, mechanical thrombectomy, and reduced disability due to stroke where this treatment is available. The widespread availability of IVT is a mark of success for researchers, stroke physicians and health care planners.

However, the use of IVT varies across Europe, and demonstrates the 'inverse care law'[2]: in those areas of Europe where disability due to stroke in the mid-years of life is the highest, IVT use is amongst the lowest. Those people who live in more rural areas, outside University centres with large hospitals and in countries with more modest incomes have less access to IVT, a marker of access to acute stroke care.[3] Another reason for the low IVT treatment rates in acute ischaemic stroke patients may be related to the strict inclusion and exclusion criteria of pivotal randomized controlled clinical trials.

A well-functioning health care system is needed to provide rapid IVT to patients with acute stroke: emergency dispatch centres, primary care, ambulance services, emergency departments, radiologists, and stroke teams coordinated by a vascular neurologist or a stroke physician. A stroke physician needs to ensure optimal patient selection, and rapid decision making because IVT is more effective when given sooner after stroke.

Therefore, we set out to provide guidelines on the use of intravenous thrombolytics for stroke physicians in Europe. We sought to update previous guidelines from the European Stroke Organisation (ESO).[1] Since 2008, new randomised controlled clinical trials (RCTs) have added to our knowledge. Here we review and make recommendations from randomized and observational studies that support a wider use of IVT, particularly about patient selection in late time windows and in patients with relative contraindication to alteplase.

In this document, we outline the current state of the evidence on the effect of IVT in different patient subgroups and time windows, with different thrombolytic agents, and with different imaging selection strategies. We hope to facilitate decision-making in patients where there is uncertainty about eligibility for IVT.

7 - Methods

This guideline was initiated by the ESO and prepared according to the ESO standard operating procedure, [4] which is based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system. [5] The ESO Guideline Board and Executive Committee reviewed the intellectual and financial disclosures of all module working group (MWG) members (Supplemental Table 1) and approved the composition of the group, which was chaired by Eivind Berge and William Whiteley up to January 2020. Following the sad death of Eivind Berge, the MWG was chaired by Guillaume Turc and William Whiteley.

The steps undertaken by the MWG are summarized as follows:

- 1. A list of topics of clinical interest to Guidelines' users was produced and agreed by all MWG members, avoiding: intra-arterial thrombolysis, mechanical thrombectomy, early secondary prophylactic treatment after IVT, service provision or delivery of treatment (e.g. thrombolysis in a spoke hospital before transfer to stroke hub ['drip and ship'], or thrombolysis in a hub hospital with rapid access to a thrombectomy suite ['mothership']), drugs other than alteplase and tenecteplase (e.g. desmoteplase, streptokinase, urokinase), stroke in children, and stroke in pregnancy or in the peripartum period.
- 2. A list of relevant outcomes was produced and the MWG used the Delphi method to score their importance (mean score from 10 respondents on a scale from 1 to 10):
- Functional outcome including death (modified Rankin Scale [mRS] scores 0-6): 8.3
- Symptomatic intracranial haemorrhage (sICH): 7.6
- Death: 7.4
- Quality of life: 6.2
- Imaging-measured recanalisation: 5.9
- Major extracranial bleeding: 5.7
- Neurological outcome (e.g. NIHSS score): 5.5
- Imaging-measured final infarct size: 4.7

Based on this vote, functional outcome was the outcome of highest priority and was considered first, followed by sICH and death. Unless specified otherwise, 'excellent' and 'good' outcome were defined as three-month mRS scores of 0–1 and 0–2, respectively. Unless specified otherwise, 'better functional outcome' corresponded to a reduction of at least one point in the mRS score at three months. sICH was defined according to each study's original criteria. In case of limited data for the outcomes of highest importance, outcomes of lesser importance were also considered.

- 3. The MWG formulated a list of Population, Intervention, Comparator, Outcome (PICO) questions, which were reviewed and subsequently approved by the ESO Guideline Board and Executive Committee.
- 4. The main recommendations were based on a systematic review of RCTs of IVT versus control. To this aim, we have updated the results of a previously published systematic review that was conducted up to March 2012.[6] We have applied the same search strategy[6] for a period from March 2012 to May 2020. We have also included relevant literature published afterwards in the final manuscript.
- 5. The authors independently screened the titles and abstracts of the publications identified by the electronic search and assessed the full text of potentially relevant RCTs.
- 6. For each PICO question, a PICO group consisting of two or three MWG members was formed. Whenever no RCT was available on a certain topic, each PICO group conducted a literature search to identify systematic reviews of non-randomized studies or key observational studies.
- 7. Whenever appropriate, random-effects meta-analyses were conducted using Stata software version 11.0 (Statacorp). Results were summarized as odds ratios (ORs) and their 95% confidence intervals (CIs). Heterogeneity across studies was assessed using the I^2 statistic. Heterogeneity was classified as moderate ($I^2 \ge 30\%$), substantial ($I^2 \ge 50\%$), or considerable ($I^2 \ge 75\%$).[7]
- 8. The results of data analysis were imported into the GRADEpro Guideline Development Tool (McMaster University, 2015; developed by Evidence Prime, Inc.). For each PICO question and each outcome, the risk of bias was assessed and quality of evidence was rated as high, moderate, low or very low based on the type of available evidence (randomized or observational studies) and considerations on inconsistency of results, indirectness of evidence, imprecision of results, and risk of bias.[5] GRADE evidence profiles/summary of

findings tables were generated using GRADEPro.

- 9. Each PICO group addressed their respective PICO question by writing up to three distinct paragraphs. First, a paragraph named 'Analysis of current evidence', in which the results of the dedicated RCTs were summarized and briefly discussed. Where no RCT was available, this paragraph described results of systematic reviews of non-randomized studies. At the end of the first paragraph, an evidence-based recommendation was provided, based on the GRADE methodology. The direction, the strength and the formulation of the recommendation were determined according to the GRADE evidence profiles and the ESO standard operating procedure. Second, an 'Additional information' paragraph could be added to provide more details on randomized trials mentioned in the first paragraph, to summarize results of observational studies, or to provide information on ongoing or future trials. Third, according to the first addendum to the ESO standard operating procedure, an 'Expert consensus statement' paragraph was added whenever the PICO group considered that insufficient evidence was available to provide evidence-based recommendations for situations in which practical guidance is needed for the everyday clinical practice. In that particular case, a pragmatic suggestion was provided, with the results of the votes of all MWG members on this proposal. Importantly, the suggestions provided in this paragraph should not be mistaken as evidence-based recommendations.
- 10. The Guideline document was subsequently reviewed several times by all MWG members and modified until a consensus was reached. Finally, the Guideline document was reviewed and approved by external reviewers and members of the ESO Guideline Board and Executive Committee.

8 - Results

8.1 - Treatment within 4.5 h of onset

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: High ⊕⊕⊕⊕

Rationale

PICO 1.1: In patients with acute ischaemic stroke of <4.5 h duration, does intravenous thrombolysis with alteplase lead to better functional outcome than no intravenous thrombolysis?

Analysis of current evidence.

Two summaries provide evidence for this question: a systematic review and meta-analysis of study-level data from 10 RCTs by Wardlaw et al. (6887 patients)[6] and an individual participant data meta-analysis from 9 RCTs by Emberson et al. (6756 patients).[8] These reviews included patients with a wide range of ages and stroke severities.

The study level meta-analysis demonstrated that alteplase within six hours of stroke onset reduced the risk of death or disability defined as a mRS score of 3–6 [odds ratio (OR) 0.84, 95% CI: 0.77–0.93, P=0.0006, I^2 =63%], and that the effect was greatest within three hours (OR 0.68, 95% CI: 0.53–0.87, P=0.002, I^2 =0.0%).

The individual participant data meta-analysis was consistent with these results. It showed that alteplase significantly increased the odds of excellent outcome (no or non-disabling symptoms, mRS score 0–1) at three months (six months in the third International Stroke Study [IST-3][9]), with earlier treatment resulting in greater proportional benefit (p for interaction =0.016). Alteplase significantly increased the odds of an excellent outcome when given within three hours (OR 1.75, 95% CI: 1.35–2.27, p<0.0001) from 3 to 4.5 h (OR 1.26, 95% CI: 1.05–1.51, P=0.0132, Figure 1), but not after 4.5 h (OR 1.15, 95% CI: 0.95–1.40, P=0.15). The overall quality of evidence was rated as high, with no serious risk of bias, inconsistency, indirectness, or imprecision (Table 1).

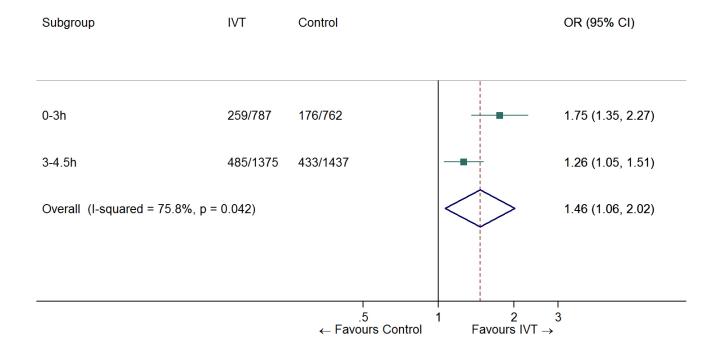


Figure 1. Pooled Odds Ratio for excellent outcome (mRS 0-1) in patients treated with IVT vs. control in the 0-4.5h time window. The numbers and the ORs for the two time subgroups are from the individual participant data meta-analysis of 9 RCTs by Emberson et al.

Additional information

The study-level systematic review showed that alteplase increased the odds of sICH (OR 3.72, 95% CI: 2.98–4.64, P=0.00001, I2=28%) and of fatal intracranial haemorrhage within 7–10 days (OR 4.18, 95% CI: 2.99–5.84, p<0.00001, I2=0.0%).[6] Although alteplase was associated with an excess of early deaths, it had no clear effect on death by the end of follow-up (OR 1.06, 95% CI: 0.94–1.20, P=0.34, I2=38%).

The meta-analysis of individual patient data showed that IVT with alteplase significantly increased the risk of sICH defined as parenchymal haemorrhage of type 2 (OR 5.55, 95% CI: 4.01–7.70, p<0.0001) or fatal haemorrhage within seven days (OR 7.14, 95% CI: 3.98–12.79, p<0.0001).[8] The absolute excess risk of intracranial haemorrhage increased with increasing stroke severity, but the absolute risk of haemorrhage was less than the benefit from treatment with alteplase at all levels of stroke severity: for the average patient treated within 4.5 h the absolute increase in the proportion of patients with a mRS score of 0 or 1 (6.8%, 95% CI: 4.0–9.5) exceeded the absolute increase in risk of fatal intracranial haemorrhage (2.2%, 95% CI: 1.5–3.0).[10]

The meta-analysis of individual patient data showed that the early excess case fatality caused by intracranial haemorrhage did not translate into a significant excess case fatality at 90 days in patients treated in the 0–4.5 h time window (HR 1.08, 95% CI: 0.94–1.24, P=0.27, Figure 2).[8] With longer follow-up, there was no evidence of reduced survival in alteplase-treated patients at 18 months,[11] and at 3 years there was a nonsignificant risk difference in favour of alteplase (risk difference 3.6%, 95% CI: –0.8 to 8.1%).[12]

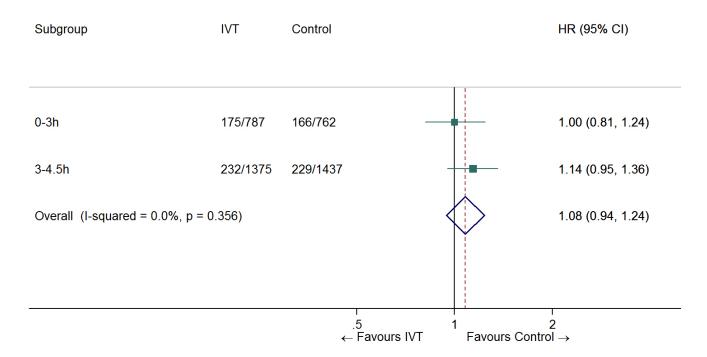


Figure 2. Pooled hazard ratio for death at three months in patients treated with IVT vs. control in the 0–4.5 h time window. The numbers and the HRs for the two time subgroups are from the individual patient data meta-analysis of nine RCTs by Emberson et al.

It has been recently argued that the evidence supporting the use of IVT 3–4.5 h after stroke is frail, and that imbalance in baseline NIHSS score may have been solely responsible for the positive results of the ECASS-3 trial.[13] However, the individual participant data meta-analysis by Emberson et al. does provide support for this time window, and did adjust for NIHSS score at baseline.[8]

Although IVT is currently recommended prior to mechanical thrombectomy,[14] there is a debate about whether IVT is necessary for patients directly arriving at stroke centre with thrombectomy capability. The recently published Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals Multicenter Randomized Clinical Trial (DIRECT-MT) suggested that direct mechanical thrombectomy alone was non-inferior to mechanical thrombectomy preceded by IVT with alteplase (0.9 mg/kg) administered within 4.5 h after symptom onset (n=656, adjusted cOR for better functional outcome at three months 1.07, 95% CI: 0.81–1.40; P=0.04).[15] However, the trial had a liberal noninferiority margin (20%); a long onset to-IVT time (median approximately 184 min); and very short delay from start of IVT to groin puncture (median approximately 29 min). In addition, alteplase was not reimbursed in the setting of DIRECT MT, which may have resulted in delaying the allowed time for consenting the patient and in further delaying the door to needle time (median 59 min). Moreover, 31 patients in the bridging therapy (IVT plus mechanical thrombectomy) group did not receive endovascular thrombectomy, while another 30 patients from the same group did not receive any or the full-dose of alteplase.[16] The

proportion of patients with successful reperfusion after thrombectomy (eTICI \geq 2 b) was 79.4% vs. 84.5% (OR 0.70, 95% CI: 0.47–1.06) in the direct mechanical thrombectomy and the bridging therapy groups, respectively. sICH occurred in 4.3% and 6.1% of patients in the direct thrombectomy and bridging therapy groups, respectively (OR 0.70, 95% CI: 0.36–1.37). Other trials comparing direct mechanical thrombectomy and bridging therapy in mothership patients with large vessel occlusion are ongoing (NCT03192332, NCT03494920, ISRCTN80619088).

Whether IVT is effective in patients with lacunar stroke has been debated. In the subgroup of patients with clinically defined lacunar infarct in the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial (13% of enrolled patients), the OR for excellent outcome was 2.53 (95% CI: 1.00–6.37; P=0.047).[17] In patients with clinically defined lacunar infarct in IST-3 (11% of enrolled patients), the adjusted OR for good functional outcome at six months was 0.91 (0.48–1.72). However, there was no evidence of heterogeneity of the effect of IVT across stroke clinical syndromes (P for interaction=0.46).9 In a post-hoc analysis of participants with MRI-defined lacunar stroke from the Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial (21% of included patients), the OR for excellent outcome was 1.68, 95% CI: 0.78–3.69, without evidence of heterogeneity of the effect of IVT in participants with lacunar stroke or other stroke types (P for interaction=0.94).[18]

Vessel occlusion status was not available for the majority of patients included in pivotal trials of IVT vs. no IVT, in which the imaging modality of choice was plain CT. In IST-3, there was a non-significant trend toward a better effect of IVT in patients with obstructed (cOR for better functional outcome 1.86; 95% CI: 0.76–4.53) versus patent (OR, 0.72; 95% CI: 0.42–1.25) arteries (P for interaction=0.075).[19] However, the number of patients without arterial occlusion was modest (n=140). A study-level metaanalysis suggested a significant interaction, but the thrombolytic used in 3 of the 5 included RCTs was desmoteplase rather than alteplase.[19] A post-hoc analysis of the WAKE-UP trial was presented at the ESO Conference in 2019 but has not been published yet.[20] Among patients who underwent time-of-flight magnetic resonance angiography (96% of the whole cohort), a total of 308 (63%) patients did not have visible arterial occlusion after assessment by a core lab. There was no evidence of modification of the effect of alteplase by the presence or absence of visible vessel occlusion (OR for mRS 0–1 at three months: 2.04, 95% CI: 1.00–4.18 and 1.58, 95% CI: 0.97–2.56, respectively; P for interaction=0.56).

In summary, IVT increases the risk of intracranial haemorrhage and early death, but for those treated within 0–4.5 h there are no clear excess of deaths by 90 days. Although there are ongoing discussions about the use of IVT in acute stroke in particular circumstances – before thrombectomy, in patients with lacunar stroke, and in patients with no visible large artery occlusion – there is currently no strong evidence that it should be avoided.

Clinical Question/ PICO

Population: Patients with acute ischaemic stroke of <4.5 h duration

Intervention: Intravenous thrombolysis with alteplase

Comparator: No intravenous thrombolysis

Outcome Timeframe	Study results and measurements	No intravenous	ect estimates Intravenous thrombolysis with alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
mRS 0-1 three months	Odds Ratio 1.46 (CI 95% 1.06 - 2.02) Based on data from 4,361 patients in 9 studies. (Randomized controlled)		344 per 1000 more per 1000 ore - 159 more)	High	Intravenous thrombolysis with alteplase increases excellent outcome (mRS score 0–1) compared to no intravenous thrombolysis.
Death three months	Hazard Ratio 1.08 (CI 95% 0.94 - 1.24) Based on data from 4,361 patients in 9 studies. (Randomized controlled)		188 per 1000 more per 1000 wer - 38 more)	High	There is little or no difference between intravenous thrombolysis with alteplase and no intravenous thrombolysis in death rate.

8.2 - Treatment between 4.5 and 9 h after known onset without use of advanced imaging

Strong recommendation against

For patients with acute ischaemic stroke of 4.5–9 h duration (known onset time), and with no brain imaging other than plain CT, we recommend no intravenous thrombolysis.

Quality of evidence: Moderate ⊕⊕⊕

Rationale

PICO 2.1 In patients with acute ischaemic stroke of 4.5-9 h duration (known onset time) selected with plain CT, does intravenous thrombolysis with alteplase lead to better functional outcome than no intravenous thrombolysis?

Analysis of current evidence.

The great majority (98.5%) of patients included in an individual participant meta-analysis of 9 RCTs were randomized after brain imaging with plain CT.[8] In 6 RCTs, patient could be randomized beyond 4.5 h and up to 6 h after symptom onset (1229 patients treated with alteplase vs. 1166 receiving placebo).[9][21][22][23][24][25] This individual participant data meta-analysis showed no evidence of significant benefit of alteplase compared to placebo after 4.5 h of stroke onset or when last seen well (OR for excellent outcome at 3–6 months: 1.15, 95% CI: 0.95–1.40).[8] Qualitatively similar results were obtained for good outcome (mRS 0–2), and with an ordinal logistic regression model (cOR for better functional outcome beyond 4.5 h: 1.03, 95% CI: 0.90–1.18).[26] The time at which the lower 95% CI for the estimated treatment benefit (mRS 0–1) crossed 1.0 was estimated to be 5.1 h.[8]

In a study level meta-analysis, the 4.5 h threshold was not examined specifically,[6] but there was no significant effect of alteplase in patients randomised more than three hours after stroke (OR 0.97, 95% CI: 0.85–1.09; 5 trials, 1449 participants, 12=45%), although this estimate was not statistically different from patients randomised less than three hours after stroke.

The increase in risk of fatal ICH or type 2 parenchymal hemorrhage with alteplase in comparison with placebo was similar

irrespective of treatment delay.[8] In patients treated more than 4.5 h after stroke, the OR for parenchymal haemorrhage type 2 with alteplase was 6.89 (95% CI: 4.17–11.38), similar to what is observed for patients treated within 4.5 h from symptom onset (OR 5.58, 95% CI: 3.35–9.30).[27] Using the SITS-MOST definition of symptomatic intracranial haemorrhage, the absolute excess risk of intracerebral haemorrhage with alteplase was 3.1% within three hours (95% CI: 1.7–5.2), 3.0% between 3 and 4.5 h (95% CI: 1.6–5.0), and 3.6% (95% CI: 2.0–6.0) beyond 4.5 h (p-value for interaction 0.73).[10] In patients treated more than 4.5 h after stroke onset, IVT with alteplase led to a non-significant higher three-month mortality (HR: 1.22; 95% CI: 0.99–1.50).[8]

Other studies have found that patient selection using a prognostic score based on simple clinical variables and plain CT alone cannot identify a patient population for which alteplase given between 4.5 and 6 h of stroke is safe or effective. [28]

Because the evidence in this chapter is from a subgroup of high-quality RCTs, we have downgraded the quality of evidence from high to moderate.

8.3 - Treatment between 4.5 and 9 h after known onset with the use of advanced imaging

Strong recommendation

For patients with ischaemic stroke of 4.5–9 h duration (known onset time) and with CT or MRI core/ perfusion mismatch*, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

*In the individual participant data meta-analysis by Campbell et al.,[34] core/perfusion mismatch was assessed with an automated processing software and defined as follows:

- 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 µm2/s (Diffusion MRI)

[†]Tmax >6 s (perfusion CT or perfusion MRI)

For patients with no CT or MRI core/perfusion mismatch, please see the expert consensus statement below.

Rationale

PICO 3.1 In patients with ischaemic stroke of 4.5-9 h duration (known onset time), and with CT or MRI core/perfusion mismatch, does intravenous thrombolysis with alteplase lead to better functional outcome than no intravenous thrombolysis?

Analysis of current evidence.

Mismatch between noncontrast CT and CT Perfusion (CTP), or between diffusion-weighted and perfusion-weighted MRI (DWI and PWI) may quantify the penumbral cerebral tissue and could identify patients who benefit of alteplase beyond 4.5 h. However, most RCTs of IVT in later time windows allowed not only the inclusion of patients with known onset >4.5 h but also of patients with wake-up stroke (unknown onset, time last seen well >4.5 h).[29][30] We decided to provide distinct recommendations for these two different clinical situations, because the true stroke onset of patients awakening from sleep may frequently be<4.5 h before randomisation.[31][32] This PICO question focuses on patients with known stroke onset 4.5–9 h before presentation.

The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) randomised 101 patients with ischaemic stroke with 3–6 h duration to alteplase or placebo. MRI was performed in all patients, but the imaging results were not used for patient selection.

Overall, 85 patients (86%) had PWI-DWI mismatch, but the trial did not demonstrate a clinical benefit of alteplase. [25] A pooled analysis of the EPITHET trial and an observational study showed that, among patients with PWIDWI mismatch within 3–6 h of symptom onset (101 patients), those treated with alteplase (60 patients) had significantly smaller infarct growth and higher reperfusion rate, but clinical outcomes were not different between the two groups. [33]

The fourth European Cooperative Acute Stroke Study (ECASS-4) compared alteplase with placebo in 119 patients presenting between 4.5 and 9 h after stroke onset or after awakening with stroke, and used MRI core/perfusion mismatch to select patients for treatment.[30] Inclusion criteria were infarct core volume <100 ml, absolute perfusion lesion volume ≥20 ml (at Tmax >6 s) and mismatch ratio between perfusion and core >1.2. This RCT stopped early when recruitment dropped after publication of the positive thrombectomy trials. Of the 119 included patients, 37 (31%) had known stroke duration of 4.5–9 h (median time to treatment 6.9 h), and 82 (69%) had woken with stroke. There was no significant effect of alteplase on better functional outcome at three months (cOR 1.20, 95% CI: 0.63–2.27, P=0.57). The treatment effect was similar in the dichotomized mRS analysis for excellent outcome (mRS 0–1) which showed a 6.4% absolute difference in favour of alteplase that did not reach statistical significance (P=0.45). No analysis of the subgroup of patients with known onset time has been presented.

The Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial compared alteplase with placebo in 225 patients presenting between 4.5 and 9 h after stroke onset or after awakening with stroke, using CT or MRI core/perfusion mismatch to select patients.[29] Inclusion criteria were infarct core volume \leq 70 ml, absolute perfusion lesion volume of >10 ml and mismatch ratio between perfusion and core >1.2. Of the 225 included patients, 79 (35%) had stroke duration of 4.5–9 h, and 146 (65%) had woken with stroke. The study showed that IVT with alteplase was associated with higher proportion of patients with excellent outcome (mRS 0–1 at three months: 35.4% alteplase vs. 29.5% placebo, adjusted RR 1.44, 95% CI: 1.01–2.06, P=0.04), and there was no evidence that the effect was different in patients treated during different time intervals (4.5–6 h or 6–9 h), or in patients with wake-up stroke. A secondary pre-specified ordinal analysis did not show a significant difference in functional outcome (cOR for better functional outcome, 1.55, 95% CI: 0.96–2.49). The risk of sICH was higher in the alteplase group (adjusted RR 7.22, 95% CI: 0.97–53.5, P=0.05).

Campbell et al.34 conducted an individual participant data meta-analysis of EPITHET,[25] ECASS-4[30] and EXTEND.[29] The main analysis was based on all patients who met the inclusion criteria of the original studies (n=414; 52% imaged with perfusion-diffusion MRI, 48% with perfusion CT). IVT led to a higher rate of excellent outcome (36% alteplase vs. 29% placebo, OR 1.86, 95% CI: 1.15–2.99, P=0.01), higher rate of symptomatic intracerebral hemorrhage (5% vs.<1%; OR 9.7, 95% CI: 1.23–76.55, P=0.03) with no significant difference in mortality (14% vs. 9%; OR 1.55, 95% CI: 0.81–2.96, P=0.19).[34] However, 51% of included patients had woken with stroke. There was no evidence of a modification of the effect of alteplase in an analysis across the 3 predefined time strata (4.5–6 h, 6–9 h, wake-up stroke; P for interaction=0.87). In the subgroups of patients with known onset treated between 4.5–6 h and 6–9 h, the ORs for excellent outcome (mRS score 0–1) were 2.19 (95% CI: 0.82–5.85) and 2.27 (95% CI: 0.83–6.24), respectively. Similar results were observed for good outcome and better functional outcome (Figure 3).

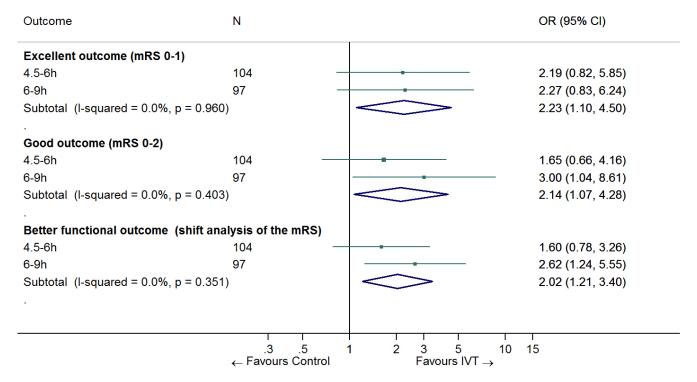


Figure 3. Pooled odds ratio for excellent outcome (mRS 0–1), good outcome (mRS 0–2) and better functional outcome (common OR across the whole range of the mRS) in patients with ischaemic stroke of 4.5–9 h duration (known onset time) treated with IVT vs. control. This analysis comprises all patients enrolled in the EXTEND, ECASS 4 and EPITHET trials, stratified by time window (4.5–6 h and 6–9 h).

The numbers and the ORs for the 4.5–6 h and 6–9 h time windows (adjusted on age and baseline NIHSS score) are taken from the individual patient data meta-analysis of three RCTs (EXTEND, ECASS 4 and EPITHET) by Campbell et al.

The authors conducted a sensitivity analysis restricted to the subgroup of 303 patients who met the mismatch criteria of the EXTEND trial (see above). To this aim, imaging data for individual patients were reprocessed using an automated software. Alteplase remained associated with excellent outcome (OR 2.06, 95% CI: 1.17–3.62). However, after exclusion of patients with wake-up stroke, the associations between IVT and excellent outcome, good outcome or better functional outcome failed to reach statistical significance (Figure 4).

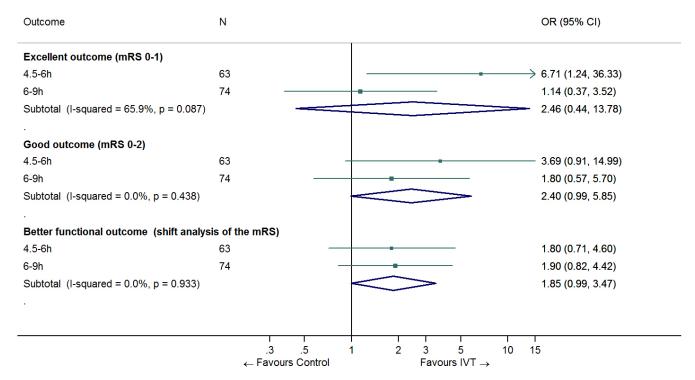


Figure 4. Pooled odds ratio for excellent outcome (mRS 0–1), good outcome (mRS 0–2) and better functional outcome (common OR across the whole range of the mRS) in patients with ischaemic stroke of 4.5–9 h duration (known onset time) treated with IVT vs. control. This analysis is restricted to the subgroup of patients enrolled in the EXTEND, ECASS 4 and EPITHET trials who meet the EXTEND mismatch criteria detected by automated software.

The numbers and the ORs for the 4.5–6 h and 6–9 h time windows (adjusted on age and baseline NIHSS score) are taken from the individual patient data meta-analysis by Campbell et al.

Of note, 62% of the patients analysed in the individual participant data meta-analysis had large vessel occlusion but no thrombectomy was performed except for 1 protocol deviation procedure.[14][34] Therefore, our evidence-based recommendation only applies to patients who will not undergo mechanical thrombectomy; please see the expert consensus statement below for patients eligible for both IVT and mechanical thrombectomy.

Table 2 provides details regarding the assessment of the quality of evidence, which was judged to be low.

Additional information

A recent prospective observational single-centre study reported that, among acute ischemic stroke patients presenting in the 0-9 h window, only 1.3% were eligible for IVT according to EXTEND neuroimaging and clinical eligibility criteria.[35]

The concept of DWI-FLAIR-mismatch, i.e., presence of an acute ischaemic lesion on DWI in the absence of a hyperintense lesion on FLAIR in the same area, has not been evaluated in RCTs of IVT for the selection of patients with known stroke duration of >4.5 h. One small observational study suggested similar functional outcomes in patients treated within 4.5 h and patients selected with the use of DWI-FLAIR mismatch and treated between 4.5 and 6 h after stroke onset.[36]

There is no current RCT assessing whether IVT is superior to no IVT in patients who undergo advanced imaging and display no core/perfusion mismatch. In the subgroup of patients who did not meet the EXTEND mismatch criteria after reprocessing imaging data with an automated software in the individual participant data meta-analysis by Campbell et al. (see above),[34] no significant difference was observed in the proportions of patients who achieved excellent functional outcome between the alteplase and placebo groups (adjusted OR 1.22, 95% CI: 0.48–3.10, P=0.68), but there was no significant treatment by mismatch status interaction (P=0.43). These results should be interpreted with caution because those patients were still considered to have a core/ perfusion mismatch according to an alternative definition of penumbral mismatch (i.e., they were

deemed to meet the inclusion criteria of the RCT in which they were enrolled). Furthermore, the above-mentioned analysis also encompasses patients with wake-up stroke.

There is currently no randomized data to make a recommendation for patients who are scheduled to undergo mechanical thrombectomy and are also eligible for IVT in the 4.5–9 h time window.

Consensus recommendation

Expert consensus statement

For patients with ischaemic stroke of 4.5–9 h duration (known onset), and with no CT or MRI core/ perfusion mismatch, 9 of 9 group members suggest against IVT with alteplase.

Rationale

There is no current RCT assessing whether IVT is superior to no IVT in patients who undergo advanced imaging and display no core/perfusion mismatch. In the subgroup of patients who did not meet the EXTEND mismatch criteria after reprocessing imaging data with an automated software in the individual participant data meta-analysis by Campbell et al. (see above),[34] no significant difference was observed in the proportions of patients who achieved excellent functional outcome between the alteplase and placebo groups (adjusted OR 1.22, 95% CI: 0.48–3.10, P=0.68), but there was no significant treatment by mismatch status interaction (P=0.43). These results should be interpreted with caution because those patients were still considered to have a core/ perfusion mismatch according to an alternative definition of penumbral mismatch (i.e., they were deemed to meet the inclusion criteria of the RCT in which they were enrolled). Furthermore, the above-mentioned analysis also encompasses patients with wake-up stroke.

Consensus recommendation

Expert consensus statement

For patients presenting directly to a thrombectomy centre with ischaemic stroke of 4.5–9 h duration (known onset) with CT or MRI core/perfusion mismatch and who are eligible for mechanical thrombectomy, the group members could not reach a consensus regarding whether intravenous thrombolysis should be used before mechanical thrombectomy.

For patients presenting to a non-thrombectomy centre with ischaemic stroke of 4.5–9 h duration (known onset) with CT or MRI core/perfusion mismatch and who are eligible for mechanical thrombectomy, 6 of 9 group members suggest intravenous thrombolysis before mechanical thrombectomy.

8.4 - Stroke on awakening from sleep/unknown onset

Strong recommendation

For patients with acute ischaemic stroke on awakening from sleep, who were last seen well more than 4.5 h earlier, who have MRI DWI-FLAIR mismatch, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: High ++++

Rationale

PICO 4.1 In patients with acute ischaemic stroke on awakening from sleep/unknown onset, does intravenous thrombolysis with alteplase lead to better functional outcome than no intravenous thrombolysis?

Analysis of current evidence.

Up to one in five strokes occur during sleep, but IVT is often withheld in patients with new stroke symptom upon awakening and who were last seen well more than 4.5 h earlier.[37][38] Our literature search identified five randomisedcontrolled trials of IVT with alteplase in patients with wake-up stroke.[29][30][39][40][41][42]

MRI: DWI/FLAIR mismatch

The WAKE-UP trial included 503 patients who woke up with a new stroke and were last known to be well more than 4.5 h earlier, and had an acute ischaemic lesion on DWI but no marked parenchymal hyperintensity on FLAIR (DWI-FLAIR mismatch).[39][43] The trial excluded patients for whom thrombectomy was planned. Patients were randomised to alteplase 0.9 mg/kg or placebo, and the primary endpoint was excellent outcome (mRS 0-1 at 90 days). The trial was terminated prematurely owing to cessation of funding after the enrolment of 503 of an anticipated 800 patients. Thirty-four percent of the patients had an intracranial vessel occlusion. The adjusted OR for excellent outcome with alteplase was 1.61 (95% CI: 1.09–2.36, P=0.02) and the cOR for better functional outcome was 1.62 (95% CI: 1.17–2.23, P=0.003). Alteplase was also associated with a non-significantly increased risk of sICH (2.0% vs. 0.4%, P=0.15) and a non-significantly higher mortality at 90 days (4.1% vs. 1.2%, P=0.07).

The Thrombolysis for Acute Wake-Up and Unclear- Onset Strokes With Alteplase at 0.6 mg/kg (THAWS) trial used the same criteria for patient selection as the WAKE-UP trial, and patients with DWI-FLAIR mismatch on MRI were randomised to low-dose alteplase (0.6 mg/kg) or placebo.[44] The trial was terminated early following the positive results of WAKE-UP with recruitment of 131 of the planned 300 patients, leading to a low statistical power. This trial found no difference in excellent outcome (mRS score 0–1) at three months between the alteplase and control groups (RR 0.97, 95% CI: 0.68–1.41, P=0.89). There was also no difference for death (RR 0.85, 95% CI: 0.06–12.58, P>0.99). Only 1 patient in the alteplase group had sICH versus 0 in the placebo group.

The EXTEND trial compared alteplase with placebo in 225 patients presenting between 4.5 and 9 h after stroke onset (or

CT or MRI: core/perfusion mismatch

between 3 and 9 h, depending on national guidelines) or after awakening with stroke (if within 9 h from the midpoint of sleep),[29] using CT or MRI core/perfusion mismatch to select patients. Inclusion criteria were infarct core volume ≤70 ml, absolute perfusion lesion volume of >10 ml and mismatch ratio between perfusion and core >1.2. After 225 of the planned 310 patients had been enrolled, the study was terminated because of a loss of equipoise after the publication of the WAKE-Up trial. The study found that alteplase was associated with excellent outcome (mRS 0−1 at 90 days: adjusted RR 1.44, 95% CI: 1.01−2.06, P=0.04). Of note, the study would not have demonstrated superiority of alteplase had the investigators used another method of analysis than adjusted Poisson regression and a primary endpoint of mRS 0−1. However, the statistical analysis plan was determined before database lock and the results are therefore valid. Intervention and control groups were generally well balanced, but alteplase-treated patients were slightly older, and with more severe strokes as measured by both core volume and NIHSS score and this may account for the lack of statistical significance for primary and secondary clinical endpoints in the unadjusted analyses.[45] The risk of sICH was higher in the alteplase group (adjusted RR 7.22, 95% CI: 0.97−53.5, P=0.05). The treatment effect was not significantly different across the three time strata (4.5−6 h; 6−9 h; wake-up stroke: P for interaction=0.41). A total of 146 (65%) patients had woken with

Individual participant data Meta-analysis

A systematic review and individual participant data meta-analysis of RCTs of IVT with alteplase for patients with stroke of unknown time of onset guided by advanced imaging was recently conducted by the Evaluation of unknown Onset Stroke thrombolysis trials (EOS) investigators.[46] A total of 843 patients enrolled in studies based on DWI-FLAIR mismatch (WAKE-UP[39] and THAWS[44]) or core/perfusion mismatch (EXTEND[29] and ECASS-4[30]) were included. Perfusion data was automatically reprocessed using the RAPID software, and the authors used the definition of penumbral mismatch from the EXTEND trial for their analysis (infarct core volume ≤70 ml, absolute perfusion lesion volume of >10 ml and mismatch ratio between perfusion and core >1.2). The median time between last seen well and treatment initiation was 10.5 h and the imaging modality was MRI in 85% of cases. Compared to placebo or standard care, IVT was significantly associated with excellent

stroke. In the subgroup of patients with wake-up stroke, the adjusted RR for excellent outcome was 1.53 (95% CI: 0.97-2.43).

outcome (primary endpoint: adjusted OR 1.49, 95% CI: 1.10–2.03, P=0.01; I2=27%) and better functional outcome (adjusted cOR 1.39, 95% CI: 1.05–1.80, P=0.02), at the expense of a higher risk of sICH (3% vs. 0.5%, P=0.02) and mortality within three months (adjusted OR 2.06, 95% CI: 1.03–4.09, P=0.04). The effect of alteplase was consistent across predefined subgroups, including imaging modality (CT vs. MRI) and large vessel occlusion status. Of note, mechanical thrombectomy was not performed in the 25% of included patients with large vessel occlusion.

Albeit based on the EOS meta-analysis, our recommendation for patients with MRI DWI-FLAIR mismatch is mostly driven by the results of the WAKE-UP trial, which used a standard dose of alteplase, unlike the small THAWS trial, in which the dose of 0.6 mg/kg was used. Both studies were terminated early. We rated the quality of the evidence as high (Table 3) because of the relatively large sample size, the fact that the WAKE-UP study was specifically focusing on patients with unknown symptom onset and that the superiority of IVT was consistently observed across secondary endpoints. For patients with CT or MRI perfusion core/perfusion mismatch and unknown time of onset, we rated the quality of evidence as moderate (Table 3) for several reasons. First, no study based on perfusion mismatch was specifically dedicated to patients with unknown time of onset and therefore the evidence comes from subgroups of patients in two relatively small RCTs that were stopped prematurely. Second, the positive association between IVT and excellent outcome was only demonstrated after a reanalysis of individual patient imaging data using the perfusion criteria of the EXTEND trial,[29] which slightly differ from those of the ECASS 4 trial.[30] Based on the perfusion mismatch criteria of each original study, the association would not have been significant (OR 1.56; 0.81–3.02).34 Of note, in the EOS individual participant data meta-analysis, only 54% (n=221) of patients with available assessment for perfusion imaging had a penumbral mismatch according to the EXTEND criteria[46]. However, because this analysis showed a clear benefit of IVT (adjusted OR for excellent outcome 2.14, 95% CI: 1.11–4.12), we provide a strong recommendation in favour of IVT in this situation.

There is currently no randomized data to make a recommendation for wake-up stroke patients who are scheduled to undergo mechanical thrombectomy and are also eligible for IVT; please see the expert consensus statement below for this situation.

Additional information

As of September 2020, two trials on intravenous thrombolytic treatment in patients with a wake-up stroke are ongoing (NCT03181360 [TWIST], and NCT01455935 [WASSABI]).

Strong recommendation

For patients with acute ischaemic stroke on awakening from sleep, who have CT or MRI core/perfusion mismatch* within 9 h from the midpoint of sleep, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate +++

*In the EOS individual participant data meta-analysis,[46] core/perfusion mismatch was assessed with an automated processing software and defined as follows:

- 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 mm2/s (Diffusion MRI)
- [†] Tmax >6 s (perfusion CT or perfusion MRI)

Rationale

Please click on "Rationale" under the recommendation for DWI-FLAIR mismatch.

Consensus recommendation

Expert consensus statement

For patients presenting directly to a thrombectomy centre with acute ischaemic stroke on awakening from sleep, who would be eligible for both IVT and mechanical thrombectomy, 6 of 9 group members suggest IVT before MT.

For patients presenting to a non-thrombectomy centre with acute ischaemic stroke on awakening from sleep, who would be eligible for both IVT and mechanical thrombectomy, 7 of 9 group members suggest IVT before MT.

8.5 - Tenecteplase

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration and not eligible for thrombectomy, we suggest intravenous thrombolysis with alteplase over intravenous thrombolysis with tenecteplase. Please see PICO 5.2 for patients eligible for mechanical thrombectomy.

Quality of evidence: Low ++

Rationale

PICO 5.1 In patients with acute ischaemic stroke of <4.5 h duration, does IVT with tenecteplase lead to better functional outcome than IVT with alteplase?

Analysis of current evidence.

Tenecteplase has pharmacological advantages over alteplase. It has a higher fibrin affinity, longer half-life, and can be administered with a single intravenous bolus injection. We identified 3 RCTs comparing tenecteplase with alteplase in 'unselected' patients with acute ischaemic stroke,[47][48][49] which are reviewed in the present section, and two trials comparing tenecteplase with alteplase in selected patients with acute ischaemic stroke due to large vessel occlusion, which are discussed in the next section (PICO 5.2) in order to limit heterogeneity in meta-analyses.[50][51]

In the Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke (TNK-S2B), 112 patients were randomised within three hours of stroke onset to tenecteplase 0.1 mg/kg, 0.25 mg/kg, 0.4 mg/kg, or alteplase 0.9 mg/kg. The first step of the trial aimed at finding the optimal dose of tenecteplase using a composite outcome measure, and the second step aimed at testing whether this dose was superior to alteplase 0.9 mg/kg in improving functional outcome at three months.[47] The trial was terminated prematurely because of slow recruitment. The adaptive dose selection procedure suggested that tenecteplase 0.4 mg/kg was inferior to the two other doses due to an excess of sICH (incidence rate 15.8%, 95% CI: 5.5–37.6%). The proportion of patients with good functional outcome (mRS 0–2) at three months did not differ between the treatment arms, but the study was underpowered for this analysis.

In the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) trial, 104 patients were randomised to tenecteplase 0.25 mg/kg or alteplase 0.9mg/kg within 4.5 h of stroke onset.[48] The primary outcome measure was the percentage of penumbra salvaged at 24–48 h, defined as CT perfusion-defined penumbra volume at baseline minus plain CT infarct volume at 24–48 h. Three-quarters of patients had an arterial occlusion on CT angiography. Mechanical

thrombectomy was not performed. There were no significant differences for the primary outcome measure or for the secondary outcome measures of mRS scores 0–1 at 90 days (OR 1.1, 95% CI: 0.3–3.5) or sICH.

In the Norwegian Tenecteplase Stroke Trial (NOR-TEST), 1100 patients were randomised to tenecteplase 0.4 mg/kg or alteplase 0.9 mg/kg within 4.5 h of stroke onset or awakening with stroke.[49] The trial aimed to show superiority for tenecteplase, and the primary outcome measure was excellent outcome at threemonths (mRS score 0–1). The included patients had mild strokes (median NIHSS score 4) and 18% of the patients had a stroke mimic. There was no difference in the proportion of patients with excellent outcome (OR 1.08, 95% CI: 0.84–1.38, P=0.52), and there was no significant difference in the incidence of sICH.

We performed a meta-analysis of study-level data, and found no significant difference between tenecteplase and alteplase in the proportion of patients with excellent (Figure 5) or good outcome at three months (data not shown), irrespective of the tenecteplase dose. There was no significant difference in the incidence of sICH (Figure 6). A published meta-analysis also found similar functional outcomes in the two treatment groups.[52]

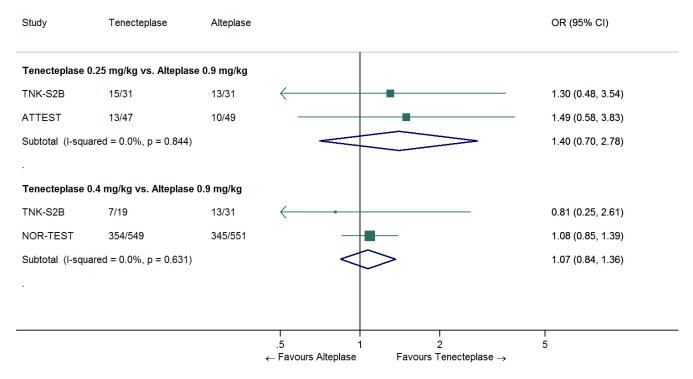


Figure 5. Pooled odds ratio for excellent outcome (mRS 0–1) in 'unselected' patients with ischaemic stroke of<4.5 h duration, treated with tenecteplase (0.25 or 0.4 mg/kg) vs. alteplase (0.9 mg/kg).

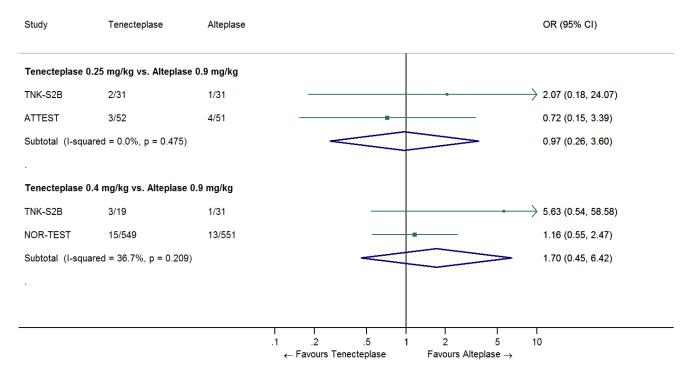


Figure 6. Pooled odds ratio for sICH in 'unselected' patients with ischaemic stroke of < 4.5 h duration, treated with tenecteplase (0.25 or 0.4 mg/kg) vs. alteplase (0.9 mg/kg).

The quality of the evidence was deemed low (see Table 4 for justification). None of the trials were designed to show non-inferiority of tenecteplase compared to alteplase.

Additional information

A meta-analysis of 5 randomized trials (TNK-S2B, Tenecteplase versus Alteplase for Acute Ischemic Stroke [TAAIS], ATTEST, NOR-TEST, Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke [EXTEND-IA TNK]) suggested that there is enough evidence to conclude that tenecteplase is non-inferior to alteplase for acute ischemic stroke (risk difference for mRS 0–1: 4%, 95% CI: –1% to 8%).[53] However, this result was mostly driven by the inclusion of EXTEND-IA TNK and TAAIS in the meta-analysis, which enrolled only patients with large vessel occlusion as opposed to the other trials. Furthermore, the high proportion of stroke mimics in NOR-TEST could have biased results towards non-inferiority. Of note, the non-inferiority margin was selected using data from a RCT comparing two doses of alteplase (0.9 mg/kg vs. 0.6 mg/kg).[54]

There are ongoing trials of tenecteplase for acute ischemic stroke (ATTEST-2 [NCT02814409], Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation (TASTE; ACTRN12613000243718), A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion (TEMPO-2; NCT02398656). We encourage enrolment into ongoing trials.

Clinical Question/ PICO

Population: 'Unselected' patients with acute ischaemic stroke of<4.5 h duration

Intervention: IVT with tenecteplase 0.25mg/kg
Comparator: IVT with alteplase 0.9 mg/kg

Outcome Timeframe	Study results and measurements	Absolute effective live with alteplase 0.9 mg/kg	ct estimates IVT with tenecteplase 0.25mg/kg	Certainty of the Evidence (Quality of evidence)	Plain text summary
mRS 0-1 three months	Odds Ratio 1.4 (CI 95% 0.7 - 2.78) Based on data from 158 patients in 2 studies. (Randomized controlled)	287 per 1000 Difference: 73 n (CI 95% 67 fewer	·	Low Due to serious risk of bias, Due to serious indirectness ¹	IVT with tenecteplase 0.25mg/kg may increase excellent outcome (mRS score 0–1) compared to IVT with alteplase 0.9 mg/kg.
Death three months	Odds Ratio 0.97 (CI 95% 0.45 - 2.09) Based on data from 158 patients in 2 studies. (Randomized controlled)	175 per 1000 Difference: 4 fe (CI 95% 88 fewer	· · · · · · · · · · · · · · · · · · ·	Low Due to serious risk of bias, Due to serious indirectness ²	There may be no difference between IVT with tenecteplase 0.25mg/kg and IVT with alteplase 0.9 mg/kg in the risk of death.
sICH	Odds Ratio 1.12 (CI 95% 0.49 - 2.52) Based on data from 165 patients in 2 studies. (Randomized controlled)	61 per 1000 Difference: 7 m (CI 95% 30 few	· ·	Low Due to serious risk of bias, Due to serious indirectness ³	There may be no difference between IVT with tenecteplase 0.25mg/kg and IVT with alteplase 0.9 mg/kg in the risk of sICH.

- 1. **Risk of bias: Serious.** The TNK-S2B trial was terminated prematurely in the dose finding phase because of slow recruitment. The following phase would have investigated the superiority of Tenecteplase over Alteplase 0.9 mg/kg.. **Inconsistency: No serious. Indirectness: Serious.** Differences in populations. **Imprecision: No serious. Publication bias: No serious.**
- 2. **Risk of bias: Serious.** The TNK-S2B trial was terminated prematurely in the dose finding phase because of slow recruitment. The following phase would have investigated the superiority of Tenecteplase over Alteplase 0.9 mg/kg.. **Inconsistency: No serious. Indirectness: Serious.** Differences in populations. **Imprecision: No serious. Publication bias: No serious.**
- 3. **Risk of bias: Serious.** The TNK-S2B trial was terminated prematurely in the dose finding phase because of slow recruitment. The following phase would have investigated the superiority of Tenecteplase over Alteplase 0.9 mg/kg.. **Inconsistency: No serious. Indirectness: Serious.** Different definitions of sICH were used across studies.. **Imprecision: No serious.** Publication bias: No serious.

Clinical Question/ PICO

Population: 'Unselected' patients with acute ischaemic stroke of<4.5 h duration

Intervention: IVT with tenecteplase 0.40mg/kg

Comparator: IVT with alteplase 0.9 mg/kg

Outcome Timeframe	Study results and measurements	Absolute effective of the Absolute effective effective of the Absolute effective effet	IVT with tenecteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
mRS 0-1 three months	Odds Ratio 1.07 (CI 95% 0.84 - 1.36) Based on data from 1,150 patients in 2 studies. (Randomized controlled)	615 per 1000 Difference: 16 m (CI 95% 42 few	•	Low Due to very serious risk of bias	IVT with tenecteplase 0.40mg/kg may increase excellent outcome (mRS score 0-1) compared to IVT with alteplase 0.9 mg/kg.
Death three months	Odds Ratio 1.03 (CI 95% 0.62 - 1.72) Based on data from 1,150 patients in 2 studies. (Randomized controlled)	58 per 1000 Difference: 2 m (CI 95% 21 few)	·	Moderate Due to serious risk of bias ²	There is probably no difference between IVT with tenecteplase 0.40mg/kg and IVT with alteplase 0.9 mg/kg in the risk of death.
sICH	Odds Ratio 1.7 (CI 95% 0.45 - 6.42) Based on data from 1,150 patients in 2 studies. (Randomized controlled)	24 per 1000 Difference: 16 m (CI 95% 13 fewe	•	Low Due to serious risk of bias, Due to serious imprecision ³	IVT with tenecteplase 0.40mg/kg may increase risk of sICH compared to IVT with alteplase 0.9 mg/kg.

- 1. **Risk of bias: Very Serious.** The TNK-S2B trial was terminated prematurely in the dose finding phase because of slow recruitment. The following phase would have investigated the superiority of Tenecteplase over Alteplase 0.9 mg/kg. In NORTEST, 18% of included patients had a stroke mimic and were distributed similarly between the Tenecteplase and Alteplase arm.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
- 2. **Risk of bias: Serious.** In NOR-TEST, 18% of included patients had a stroke mimic and were distributed similarly between the Tenecteplase and Alteplase arm. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
- 3. **Risk of bias: Serious.** In NOR-TEST, 18% of included patients had a stroke mimic and were distributed similarly between the Tenecteplase and Alteplase arm.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Clinical recommendation (tenecteplase or alteplase) would markedly differ if the upper versus the lower boundary of the 95% CI of the OR represents the truth.. **Publication bias: No serious.**

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom intravenous thrombolysis is considered before thrombectomy, we suggest intravenous thrombolysis with tenecteplase 0.25 mg/kg over intravenous thrombolysis with alteplase 0.9 mg/kg.

Quality of evidence: Low ++

Rationale

PICO 5.2 In patients with acute ischaemic stroke of <4.5 h duration and with large vessel occlusion, who are candidates for mechanical thrombectomy, and for whom intravenous thrombolysis is considered before thrombectomy, does IVT with tenecteplase

lead to better functional outcome than IVT with alteplase?

Analysis of current evidence.

In the TAAIS trial, 75 patients were randomised to tenecteplase 0.1 mg/kg or 0.25 mg/kg or alteplase 0.9 mg/kg within 6 h of stroke onset.[50] Patient selection was based on the finding of occlusion of the anterior, middle, or posterior cerebral artery on CT angiography and a CT perfusion lesion volume that was at least 20 ml and at least 20% greater than the infarct core on CT perfusion. Mechanical thrombectomy was not performed. The two co-primary outcome measures were the percentage of the perfusion lesion that was reperfused at 24 h after treatment (as assessed by perfusion MRI) and the change on the NIHSS score between baseline and 24 h. Tenecteplase was superior to alteplase for both co-primary outcome measures. At three months, good outcome (mRS 0-2) was observed in 72% of patients in the pooled tenecteplase groups vs. 44% in the alteplase group (P=0.02). The rate of symptomatic intracerebral haemorrhage did not differ significantly between the groups. In the dose-tier analysis, tenecteplase 0.25mg/kg was associated with clinical improvement during the first 24 h and a non-significant increase in the proportion of patients with good outcome at threemonths (P=0.11). The frequency of sICH was similar in the two tenecteplase groups (4%).

The EXTEND-IA TNK trial compared tenecteplase 0.25 mg/kg with alteplase 0.9 mg/kg within 4.5 h of symptom onset in 202 patients with large vessel occlusion (internal carotid artery, first and second segments of the middle cerebral artery, or the basilar artery) who were candidates for mechanical thrombectomy.[51] The trial was designed to demonstrate non-inferiority, but after testing for non-inferiority, superiority testing was performed as pre-specified. The primary outcome measure was reperfusion greater than 50% of the involved ischaemic territory or absence of retrievable thrombus at the time of the initial angiographic assessment, and was found in 22% of the patients treated with tenecteplase versus 10% of those treated with alteplase (p for non-inferiority=0.002; p for superiority=0.03). Tenecteplase was borderline associated with better 90-day functional outcome than alteplase (cOR 1.7, 95% Cl: 1.0–2.8, P=0.04 – adjusted on age and baseline NIHSS score). There were no significant differences in the proportions of patients with good (P=0.06), excellent outcome (P=0.23) or early neurological improvement (P=0.70). Symptomatic intracerebral haemorrhage occurred in 1% of the patients in each group.

A meta-analysis of patients with large vessel occlusion in EXTEND-IA TNK and TAAIS showed that tenecteplase was associated with a higher likelihood of complete recanalisation (OR 2.01, 95% CI: 1.04–3.87, P=0.04).[52] Furthermore, Bivard et al. conducted a pooled patient subgroup analysis of TAAIS and ATTEST suggesting that tenecteplase compared to alteplase was associated with higher complete recanalization rates at 24 h (71% vs. 43%; p<0.001) and higher rates of three-month excellent outcome (mRSscores of 0–1; OR 4.82, 95% CI: 1.02–7.84, P=0.05) in 69 patients with baseline intracranial occlusion [Thrombolysis in Cerebral Infarction (TICI) grades 0–1].[55] This study also suggested that vessel occlusion status (complete vs. partial or no occlusion) was a modifier of the effect of tenecteplase – compared with alteplase – regarding three-month functional outcome (P for interaction =0.01). Some of the included patients had distal vessel occlusion and would therefore not currently be eligible for mechanical thrombectomy.[14]

We have conducted a study-level meta-analysis of EXTEND-IA TNK and the subgroup of patients with complete vessel occlusion in the pooled analysis by Bivard et al. (Figure 7).[55] The pooled OR for excellent outcome and better functional outcome were 2.42 (95% CI: 0.73–8.04) and 2.09 (1.16–3.76), respectively.

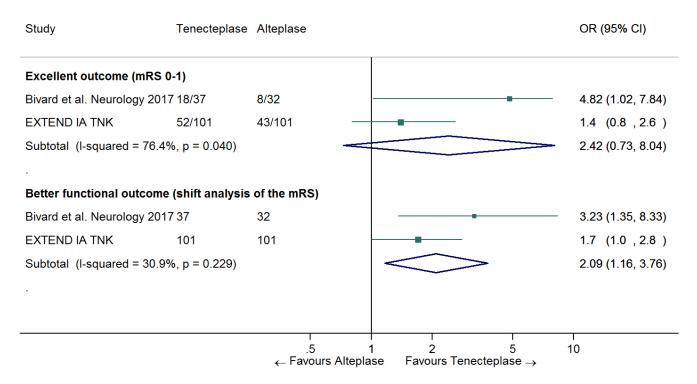


Figure 7. Pooled odds ratio for excellent outcome (mRS 0–1) and better functional outcome (common OR across the whole range of the mRS) in patients with ischaemic stroke of <4.5 h duration who have documented vessel occlusion and were randomized to IVT with tenecteplase 0.25 mg/kg vs. IVT with Alteplase 0.9 mg/kg.

The study by Bivard et al.55 is a pooled patient subgroup analysis of the TAAIS and ATTEST randomized trials. The ORs from EXTEND IA TNK were adjusted on age and baseline NIHSS score.

EXTEND-IA TNK 2 was a randomised trial comparing two different doses of intravenous tenecteplase (0.25 mg/kg vs. 0.4 mg/kg) within 4.5 h of stroke onset in 300 patients who subsequently underwent mechanical thrombectomy.[56] The proportion of patients with greater than 50% reperfusion of the previously occluded vascular territory (eTICI ≥2b50,[57] primary endpoint) before thrombectomy was 19% in the two arms. There was not difference between treatment groups regarding functional outcome at three months (adjusted common OR for better functional outcome 0.96, 95% CI: 0.74−1.24, P=0.73) and mortality. The rate of sICH according to the SITS-MOST definition was non-significantly higher in the 0.4 mg/kg arm: 4.7% vs. 1.3%, RR 3.50 (95% CI: 0.74−16.62, P=0.12).

Our recommendation is based on one small RCT, with a non-clinical primary outcome measure and a post-hoc pooled subgroup analysis of 2 other small RCTs (Figure 7). The quality of the evidence is graded as low (see Table 5 for justification).

Additional information

Tenecteplase in Stroke Patients Between 4.5 and 24 h (TIMELESS; NCT03785678) is an ongoing trial of tenecteplase versus placebo for acute ischemic stroke patients with large vessel occlusion presenting in late time windows.

Clinical Question/ PICO

Population: Patients with acute ischaemic stroke of < 4.5 h duration and with large vessel occlusion, who are candidates for mechanical thrombectomy, and for whom intravenous thrombolysis is considered before thrombectomy

Intervention: IVT with tenecteplase Comparator: IVT with alteplase

Outcome Timeframe	Study results and measurements	Absolute effect estimates IVT with alteplase IVT with tenecteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
mRS 0-1 threemonths	Odds Ratio 2.42 (CI 95% 0.73 - 8.04) Based on data from 202 patients in 3 studies. (Randomized controlled)	426 642 per 1000 per 1000 Difference: 216 more per 1000 (CI 95% 75 fewer - 431 more)	Low Due to serious inconsistency, Due to serious indirectness ¹	IVT with tenecteplase may increase excellent outcome (mRS score 0–1) compared to IVT with alteplase.
Improved mRS score three months	Odds Ratio 2.09 (CI 95% 1.16 - 3.76) Based on data from patients in 3 studies. (Randomized controlled)	CI 95%	Low Due to serious inconsistency, Due to serious indirectness ²	
Death three months	Odds Ratio 0.4 (CI 95% 0.2 - 1.1) Based on data from 202 patients in 1 studies. (Randomized controlled)	178 80 per 1000 per 1000 Difference: 98 fewer per 1000 (CI 95% 137 fewer - 14 more)	Moderate Due to serious indirectness ³	IVT with tenecteplase probably reduces the risk of death compared to IVT with alteplase.
sICH	Odds Ratio 1 (CI 95% 0.1 - 16.2) Based on data from 202 patients in 1 studies. (Randomized controlled)	10 10 per 1000 per 1000 Difference: 0 fewer per 1000 (CI 95% 9 fewer - 131 more)	Low Due to very serious imprecision ⁴	There may be no difference between IVT with tenecteplase and IVT with alteplase in the risk of sICH.

- 1. Inconsistency: Serious. In EXTEND IATNK, tenecteplase was only significantly associated with better functional outcome in shift analysis of the mRS. Furthermore, other RCTs in unselected patients did not suggest superiority of tenecteplase over alterplase.. Indirectness: Serious. This result is based on a secondary outcome of the EXTEND IATNK trial and subgroup analyses of TAAIS and ATTEST. In those last 2 trials, some patients had distal vessel occlusion (M2, M3, ACA, PCA).. Imprecision: No serious. Publication bias: No serious.
- 2. **Inconsistency: Serious.** In EXTEND IATNK, tenecteplase was only significantly associated with better functional outcome in shift analysis of the mRS. Furthermore, other RCTs in unselected patients did not suggest superiority of tenecteplase over alterplase.. **Indirectness: Serious.** This result is based on a secondary outcome of the EXTEND IATNK trial and subgroup analyses of TAAIS and ATTEST. In those last 2 trials, some patients had distal vessel occlusion (M2, M3, ACA, PCA).. **Imprecision: No serious. Publication bias: No serious.**
- 3. **Inconsistency: No serious. Indirectness: Serious.** The primary endpoint was radiological, not clinical.. **Imprecision: No serious. Publication bias: No serious.**
- 4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Only one event in each treatment group.. **Publication bias: No serious.**

8.6 - Alternative doses

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration who are eligible for intravenous thrombolysis, we recommend standard-dose alteplase (0.9 mg/kg) over low-dose alteplase.

Quality of evidence: High ⊕⊕⊕⊕

Rationale

PICO 6.1 In patients with acute ischaemic stroke of <4.5 h duration, does intravenous thrombolysis with low-dose alteplase lead to non-inferior (not worse) functional outcome compared to standard-dose alteplase?

Analysis of current evidence.

The literature search identified one RCT comparing low dose (0.6mg/kg) with standard dose (0.9mg/kg) of alteplase in 3310 patients treated with IVT within 4.5 h of stroke onset, the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED).[54] The trial aimed to show non-inferiority of the lower dose. About two-thirds of patients were from Asia. Unfavourable functional outcome (mRS scores 2–6) was seen in 53.2% in the low-dose and 51.1% in the standard-dose group, which did not demonstrate noninferiority (OR 1.09, 95% CI: 0.95–1.25, P for non-inferiority = 0.51).[58] The rate of sICH was lower in the lowdose group (1.0% vs. 2.1%, P = 0.01). Mortality at threemonths did not differ significantly between the groups (8.5% and 10.3%, respectively, P = 0.07). The pre-specified subgroup analyses did not identify patients who benefitted from the low-dose therapy.[59][60][61] but patients using antiplatelet drugs before their strokes had non-significantly better functional outcomes after lowdose alteplase than other patients (OR 0.84, 95% CI: 0.62–1.12 versus OR 1.16, 95% CI: 0.99–1.36, p for interaction = 0.053).[62][63] This association was further attenuated in analyses adjusted for potential confounders.[62][63] The evidence for this recommendation is limited to one trial. However, the trial was adequately powered to address its scientific question and we could not identify reason that would lead to downgrade the quality of evidence regarding risk of bias, inconsistency, indirectness, or imprecision. The quality of evidence was therefore rated as high. The trial did not show noninferiority of low-dose alteplase, and the recommendation is therefore strong.

Additional information

The ENCHANTED trial did not show non-inferiority of low-dose alteplase, despite the fact that almost two-thirds of the patients were from Asia (who have presumed higher risk of sICH). There was also no imbalance in the baseline characteristics that could explain the results. For example, the percentage of large-artery occlusions and successful recanalisation were similar in the two groups.

There are several older Asian registry studies that have inconsistent results regarding the optimal dose of alteplase in Asian populations. [64][65][66][67][68][69][70][71][72]

8.7 - Adjunctive therapies (i.e. antithrombotic agents, ultrasound)

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, we recommend no antithrombotic drugs within 24 h of intravenous thrombolysis over antithrombotic drugs as an adjunct therapy to intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

Rationale

PICO 7.1 In patients with acute ischaemic stroke of <4.5 h duration, does antithrombotic agents in addition to IVT lead to better functional outcome than IVT alone?

Analysis of current evidence.

Re-occlusion of a cerebral artery occurs in 14%–34% of patients who have achieved recanalisation after IVT with alteplase, and is associated with clinical deterioration and poor outcome.[73][74] It has been suggested that the use of antithrombotic agents (aspirin, glycoprotein IIb/IIIa inhibitors or thrombin inhibitors) during or after alteplase infusion might reduce the risk of re-occlusion and improve functional outcome.[75][76]

The effect of intravenous aspirin as an adjunct therapy to alteplase was tested in the Antiplatelet therapy in combination with Rt-PA Thrombolysis in Ischemic Stroke (ARTIS) trial.[77] A total of 642 patients treated with alteplase were randomly assigned to 300 mg intravenous aspirin within 90 min of alteplase bolus or to no additional treatment. Oral antiplatelet therapy was given 24 h following alteplase treatment in both groups. The trial was terminated prematurely because of an excess of sICH (assessed in a non-blinded fashion) and no evidence of benefit in the aspirin group. The OR for good outcome (mRS 0-2 at three months) with intravenous aspirin was 0.91 (95% CI: 0.66-1.26, P=0.58), and the relative risk for sICH, defined as in the third European Cooperative Acute Stroke Study (ECASS-3) trial,[78] was 2.78 (95% CI: 1.01-7.63, P=0.04). Of note, follow-up imaging was not systematically performed in patients without neurological deterioration.

Eptifibatide is a glycoprotein IIb/IIIa inhibitor that is being investigated as an adjunct to intravenous thrombolysis. One randomised-controlled trial of 94 patients compared low-dose alteplase (0.3 mg/kg and 0.45 mg/kg) combined with eptifibatide to standarddose alteplase alone, and did not raise major safety concerns (OR for any ICH with combination therapy compared to alteplase alone: 0.28, 95% CI: 0.06–1.23).[79] Another trial randomised 126 patients 4:1 to low-dose alteplase (0.6 mg/kg) plus eptifibatide or standard-dose alteplase alone, and found a nonsignificantly lower risk of sICH in the combination group (OR 0.15, 95% CI: 0.01–1.40, P=0.053).[80] The safety of eptifibatide as an adjunct to alteplase low-dose or standard-dose has also been reported in observational studies.[81][82]

We identified no RCTs of the glycoprotein IIb/IIIa inhibitor tirofiban as an adjunctive therapy to alteplase, but there are observational data hinting that tirofiban might be safe (no sICH in 14 patients treated with tirofibanpstandard-dose alteplase), although uncertainties remain[83]

Argatroban is a direct thrombin inhibitor that has been given as adjunct therapy to alteplase. One small observational study of 65 patients showed that combination therapy compared to alteplase alone had a sICH rate of 4.6% in patients with proximal cerebral artery occlusion.[84] A RCT of 90 patients treated with alteplase randomised patients to no argatroban, argatroban bolus followed by low-dose infusion of argatroban, or to argotroban bolus followed by standard-dose infusion of argatroban for 48 h.[85] No difference in the rates of sICH was observed across the three groups (10, 13 and 7%, respectively; RR (low-dose argatrobran vs alteplase alone:1.27; 95% CI: 0.32–5.05; RR (highdose argatrobran vs alteplase alone:0.60; 95% CI: 0.11–3.41), as were the proportions of patients with mRS scores 0–1 at 90 days (21, 30 and 32%, respectively; RR (low-dose argatrobran vs alteplase alone:1.50; 95% CI: 0.64–3.49; RR (high-dose argatrobran vs alteplase alone:1.63; 95% CI: 0.72–3.72). However, the small sample of this trial should be taken into account in the interpretation of these findings.

The recommendation is based on the ARTIS trial and very small randomized trials assessing safety rather than efficacy. The quality of evidence is therefore graded as low.

Additional information

The effects of eptifibatide and argatroban as adjuncts to alteplase will be further investigated in the ongoing phase Multi-arm Optimization of Stroke Thrombolysis (MOST) trial (NCT03735979). In this trial, 1200 patients treated with standard-dose alteplase within three hours of stroke onset will be randomised to intravenous argatroban, eptifibatide or placebo, and the primary effect variable is functional outcome at 90 days. Patients may also receive mechanical thrombectomy per usual care.

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, we recommend against ultrasound augmentation in patients receiving intravenous thrombolysis.

Quality of evidence: Low ++

Rationale

PICO 7.2 In patients with acute ischaemic stroke of <4.5 h duration, does ultrasound augmentation of IVT lead to better functional outcome than IVT alone?

Analysis of current evidence.

Ultrasound delivers mechanical pressure waves to the clot, exposing more thrombus surface to circulating alteplase, which may potentiate fibrinolytic activity.[86][87] Moreover, intravenous gaseous microspheres have been introduced with ultrasound as an alternative to fibrinolytic agents to recanalise discrete peripheral thrombotic arterial occlusions or acute arteriovenous graft thromboses.[86][87] Small RCTs of high-frequency ultrasound in combination with thrombolytic treatment (sometimes referred to as 'sonothrombolysis') have shown promising results in patients who did not receive mechanical thrombectomy.[88][89] The Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST) trial of transcranial ultrasound and meta-analyses of other similar studies have reported that ultrasound could at least double the chance of early recanalisation.[90][91][92] In the CLOTBUST trial of 126 patients, sonothrombolysis was also associated with a higher likelihood of excellent outcome (secondary endpoint, mRS 0−1 at three months) in the subgroup of patients with pretreatment NIHSS scores ≥10 points.[93]

These findings were not reproduced in two larger RCTs. The Norwegian Sonothrombolysis in Acute Stroke Study (NOR-SASS) randomised 183 patients with or without evidence of proximal cerebral artery occlusion and without a lower cut-off for baseline NIHSS score to contrast-enhanced high-frequency sonothrombolysis or IVT with alteplase alone (with sham ultrasound monitoring).[94][95] The primary endpoints were neurological improvement at 24 h defined as a NIHSS score of 0 or a reduction of \geq 4 points compared with baseline NIHSS, and excellent functional outcome. The trial was prematurely terminated because of a lack of funding. The rates of neurological improvement at 24 h, excellent outcome at 90 days and sICH were similar in the two groups. Only 113 out of 183 enrolled patients (61%) were treated according to study protocol in NOR-SASS.

The Combined Lysis of Thrombus using Ultrasound and Systemic Tissue Plasminogen Activator for Emergent Revascularization (CLOTBUST-ER) trial enrolled 676 patients with NIHSS scores of ≥10 points who received IVT with alteplase within 4.5 h (3 h in North America) and were randomised to ultrasound enhancement of IVT or sham.[96][97] Vascular imaging was not mandatory and mechanical thrombectomy was not performed. The primary endpoint was improvement in the mRS-score at 90 days. The trial was stopped early because of futility. The adjusted cOR for better functional outcome was 1.05 (95% CI: 0.77–1.45, P=0.74) for patients treated within three hours and 1.06 (95% CI: 0.80–1.42, P=0.67) for patients treated within 4.5 h. There was no difference in three-month mortality (OR 1.19, 95% CI: 0.74–1.92, P=0.48) or sICH (OR 1.39, 95% CI: 0.51–3.95, P=0.52).

We performed a meta-analysis of the five largest RCTs[88][89][90][95][97] and found no benefit in terms of excellent outcome (mRS score 0–1 at three months) with high-frequency ultrasound in combination with alteplase versus alteplase alone (OR 1.07, 95% CI: 0.77–1.50, P=0.68, I2=12%, Figure 8).

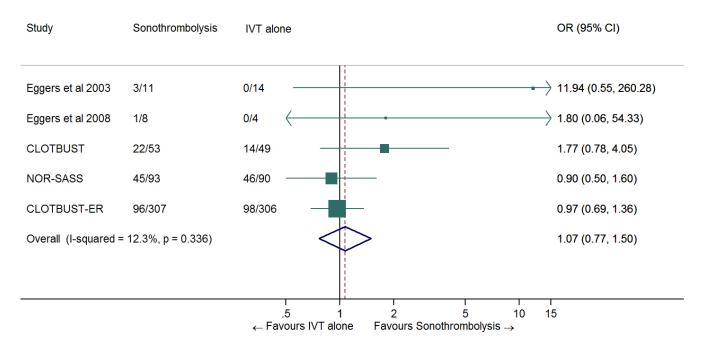


Figure 8. Pooled odds ratio for excellent outcome (mRS 0-1) in patients randomized to ultrasound augmentation of IVT vs. IVT alone. All patients received IVT with alteplase.

The recommendation is based on the results of the meta-analysis including two phase 3 and three phase 2 RCTs. The quality of evidence was judged to be low (see Table 6 for justification).

Clinical Question/ PICO

Population: Patients with acute ischaemic stroke of < 4.5 h duration

Intervention: Ultrasound augmentation of IVT

Comparator: IVT alone

Outcome Timeframe	Study results and measurements	Absolute e	ffect estimates Ultrasound augmentation of IVT	Certainty of the Evidence (Quality of evidence)	Plain text summary
mRS 0-1 three months	Odds Ratio 1.07 (Cl 95% 0.77 - 1.5) Based on data from 935 patients in 5 studies. (Randomized controlled)		356 per 1000 5 more per 1000 fewer - 96 more)	Low Due to serious risk of bias, Due to serious inconsistency ¹	Ultrasound augmentation of IVT may increase excellent outcome (mRS score 0-1) compared to IVT alone.

1. **Risk of bias: Serious.** In the CLOTBUST trial, 19% of the randomized patients were not eligible for the analysis of functional outcome at three months, which was a secondary endpoint. The two trials by Eggers et al. were very small. Furthermore, two phase III trials were stopped early.. **Inconsistency: Serious.** Two small trials by the same group (Eggers et al., 2003, 2008) and one larger study (CLOTBUST) suggested a strong benefit of sonothrombolysis, whereas two large trials did not.. **Indirectness: No serious.** Some trials only included patients with proven arterial occlusion (Eggers et al.,

CLOTBUST), whereas other studies did not (NOR-SASS, CLOTBUST-ER).. Imprecision: No serious. Publication bias: No serious.

8.8 - Higher age, multimorbidity, frailty or prior disability

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, who are over 80 years of age, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: High ⊕⊕⊕⊕

Rationale

PICO 8.1 In patients with acute ischaemic stroke of <4.5 h duration, who are over 80 years of age, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Most trials of IVT for ischaemic stroke have excluded patients who were over 80 years old or who had multimorbidity/frailty or prestroke disability. IST-3 included patients over 80 years of age and added substantial information on this patient group.[9] Information about the effect of alteplase in elderly patients can also be found in metaanalyses of RCTs, either with individual patient data[8][26][98] or on study-level.[6]

In the meta-analysis of individual participant data by Emberson et al., the OR for excellent outcome (mRS score 0–1) in patients >80 years treated with alteplase was 1.56 (95% CI: 1.17–2.08), compared to 1.25 (95% CI: 1.10–1.42) in patients ≤80 years of age, without evidence of difference in efficacy between the groups (P for interaction=0.53).[26] There was also no evidence in the pooled analysis that patients aged >80 years were at any greater risk of ICH than younger patients. Furthermore, age was not associated with increased risk of sICH in the ENCHANTED trial.[59] The Thrombolysis in Elderly Stroke Patients in Italy (TESPI) trial, which investigated IVT with alteplase within three hours of stroke onset in 191 patients over the age of 80 years, was terminated early because the IST-3 trial provided evidence of treatment benefit in in this age group.[99] The trial was underpowered and showed a non-significant effect on the proportion of good outcome (mRS score 0–2: 29% versus 23%).

The recommendation for patients who are over 80 years of age is based on an individual patient data meta-analysis of high quality.[8][98]

Consensus recommendation

Expert consensus statement

Nine of nine group members believe that age alone should not be a limiting factor for IVT, even in other situations covered in the present guidelines (e.g. wake-up stroke; ischaemic stroke of 4.5–9 h duration (known onset time) with CT or MRI core/perfusion mismatch; minor stroke with disabling symptoms).

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with multimorbidity, frailty or prestroke disability, we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Very low

Rationale

PICO 8.2 In patients with acute ischaemic stroke of <4.5 h duration, who have multimorbidity, frailty or prior disability, does intravenous thrombolysis with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

The literature search identified no trials that targeted patients with multimorbidity/ frailty or those with pre-stroke disability. An analysis of observational data from 3017 patients in IST-3 used brain imaging findings before treatment with alteplase to identify patients with pre-existing 'brain frailty', such as old lesions, brain atrophy or

leukoaraiosis. The risk of sICH was higher in patients with old infarct (OR 1.72, 95% CI: 1.18–2.51), and the chance of excellent functional outcome was lower (severe leukoaraiosis: OR 0.62, 95% CI: 0.50–0.78; severe brain atrophy: OR 0.75, 95% CI: 0.57–0.99; old infarct: OR 0.79, 95% CI: 0.64–0.96).[100] However, no imaging findings, individually or combined, modified the effect of alteplase on functional outcome or sICH.[100] Renal dysfunction, which is another marker of multimorbidity, was not associated with increased risk of sICH in the ENCHANTED trial,[60] but was associated with increased risk of other haemorrhagic complications, death and poor functional outcome before and after adjustment for potential confounders in meta-analyses of observational studies.[101][102][103][104] Finally, one observational study of patients with non-metastatic cancer, found that functional outcome after IVT with alteplase was comparable to that of other patients.[105] These findings suggest that cancer should not be an absolute contraindication against thrombolytic treatment, although caution seems appropriate.

Patients with pre-existing disability are often not treated with alteplase.[106] Despite high mortality rates, observational studies of patients with pre-existing disability have indicated that IVT may prevent further functional deterioration and that treatment is more beneficial the earlier it is given.[107][108] Observational studies have not found evidence that pre-stroke disability is associated with an increased risk of ICH after thrombolytic treatment.[107][109][110]

The recommendations for patients with multimorbidity, frailty or pre-stroke disability is based on small observational studies, corresponding to a very low quality of evidence.

Additional information

The weak recommendations given above imply that the decision to treat must be made on an individual basis and that it must consider the patient's values and preferences.

A single-centre observational study suggested that the outcome of patients with cognitive impairment no-dementia who are treated with IVT does not significantly differ from that of cognitively normal patients.[110]

8.9 - Minor stroke and stroke with rapidly improving neurological signs

Strong recommendation

For patients with acute minor, disabling ischaemic stroke of <4.5 h duration, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate ⊕⊕⊕

Rationale

PICO 9.1 In patients with acute minor, disabling ischaemic stroke of < 4.5 h duration, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

About half of all ischaemic strokes are initially minor (defined typically as NIHSS score<5), but up to one third of patients with minor stroke are disabled or dead three months after the index event.[112][113] Emberson et al. conducted an individual participant data meta-analysis of 9 RCTs of IVT with alteplase vs. placebo or open control, which included 666 patients (10%) with a baseline NIHSS score 0–4.[8] All trials included in this metaanalysis excluded patients with non-disabling neurological deficits, except IST-3.[9] The meta-analysis showed

that the proportional benefit of alteplase was not statistically different in patients with mild, moderate and severe strokes (P for interaction=0.06). In patients with baseline NIHSS score of 0-4, the OR for excellent outcome (mRS score 0-1 at three months) was 1.48 (95% CI: 1.07-2.06). These data support the use of alteplase in patients with minor disabling stroke.

One critical question is how 'minor disabling stroke' should be defined in clinical practice. No standardized definition has been used across trials included in the present meta-analysis, which relied on the subjective judgment of each investigator. An operational definition of a disabling deficit has since been proposed in the Potential of Rt-PA for Ischemic Strokes with Mild Symptoms (PRISMS) trial: 'a deficit that, if unchanged, would prevent the patient from performing basic activities of daily living (i.e., bathing, ambulating, toileting, hygiene, and eating) or returning to work'.[114]

The quality of evidence for the recommendation is moderate (see Table 7 for justification).

Clinical Question/PICO

Population: Patients with acute minor, disabling ischaemic stroke of<4.5 h duration

Intervention: IVT with alteplase

Comparator: no IVT

Outcome Timeframe	Study results and measurements	Absolute eff	fect estimates IVT with alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
mRS 0-1 three months	Odds Ratio 1.48 (CI 95% 1.07 - 2.06) Based on data from 666 patients in 9 studies. (Randomized controlled)		680 per 1000 more per 1000 ore - 158 more)	Moderate Due to serious indirectness ¹	IVT with alteplase probably increases excellent outcome (mRS score 0–1) compared to no IVT.
Fatal ICH seven days	Odds Ratio 3.9 (CI 95% 1.46 - 10.44) Based on data from 666 patients in 9 studies. (Randomized controlled)		9 per 1000 more per 1000 ore - 25 more)	Low Due to serious indirectness, Due to very serious imprecision, Upgraded due to strong association 2	IVT with alteplase may increase risk of fatal ICH compared to no IVT.

1. **Inconsistency: No serious. Indirectness: Serious.** This result is based on an analysis of subgroups of patients included in RCTs with various inclusion criteria. There was no clear definition of disabling stroke in patients with NIHSS 0-4..

Imprecision: No serious. Publication bias: No serious.

threemonth mRS score evaluations in 10% of enrolled patients.

2. Inconsistency: No serious. Indirectness: Serious. This result is based on an analysis of subgroups of patients included in RCTs with various inclusion criteria. There was no clear definition of disabling stroke in patients with NIHSS 0-4.. Imprecision: Very Serious. The number of events was extremely low.. Publication bias: No serious. Upgrade: Large magnitude of effect. strong association.

Weak recommendation against

For patients with acute minor non-disabling ischaemic stroke of <4.5 h duration, we suggest no intravenous thrombolysis. For patients with minor stroke and large-vessel occlusion, please refer to the section below (PICO 9.3).

Quality of evidence: Moderate ⊕⊕⊕

Rationale

PICO 9.2 In patients with acute minor, non-disabling ischaemic stroke of < 4.5 h duration, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Patients with minor neurological deficits (NIHSS score 0–5) judged to not be clearly disabling within three hours of stroke onset were assessed in the PRISMS trial of IVT with alteplase vs. aspirin.[114] A disabling deficit was defined as 'a deficit that, if unchanged, would prevent the patient from performing basic activities of daily living (ie, bathing/dressing, ambulating, toileting, hygiene, and eating) or returning to work'. Due to slow recruitment

and insufficient funding, the trial was terminated after inclusion of 313 patients, while the calculated sample size was 948. The adjusted risk difference for excellent outcome (mRS 0–1 at three months) with alteplase was –1.1% (95% CI: –9.4 to 7.3%) and the cOR for better functional outcome was 0.81 (95% CI: 0.5–1.2). The risk of sICH (defined as any neurological worsening within 36 h attributed to ICH by local investigators) was significantly higher in the alteplase group (risk difference 3.3%, 95% CI: 0.8–7.4), and there were more patients with serious adverse events (mostly intracranial/intracerebral hemorrhage) in the alteplase group (risk difference 12.9%, 95% CI: 4.1–21.7%). A limitation of this trial was missing

Because IST-3 had not explicitly excluded patients with non-disabling neurological deficits, we also used data from that trial.[9] Among the subgroup of patients with NIHSS 0-5 in IST-3, the adjusted OR for good functional outcome (Oxford Handicap Scale score 0-2) with alteplase was 0.85 (95% CI: 0.52-1.38).

The recommendation is based on one relatively small RCT that was stopped early and one trial that did not explicitly exclude patients with non-disabling ischaemic stroke. The quality of the evidence is therefore graded as moderate.

Additional information

A list of examples of nondisabling symptoms was provided to each participating centre in the PRISMS trial and in the published protocol [115]: isolated mild aphasia (patient still able to communicate meaningfully), isolated facial droop, mild cortical hand (especially non-dominant: NIHSS score-=0), mild hemimotor loss, hemisensory loss, mild hemisensorimotor loss and mild hemiataxia (patient till able to ambulate). Importantly, the two most common neurological deficits of patients enrolled in PRISMS were mild sensory loss (46%) and facial palsy (39%).

For patients with acute minor non-disabling ischaemic stroke of <4.5 h duration, and with proven large-vessel occlusion, there is insufficient evidence to make an evidence-based recommendation. Please see the Expert consensus statement below.

Quality of evidence: Very low

Rationale

PICO 9.3 In patients with acute minor, non-disabling ischaemic stroke of < 4.5 h duration, and with proven large vessel occlusion, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Patients with large vessel occlusion have a higher risk of stroke progression and poor prognosis than other patients.[116] The literature search identified no RCT of IVT with alteplase in patients with NIHSS scores of 0–5 with nondisabling neurologic deficits and with proven intracranial large artery occlusion. TEMPO-1 was a case series of 50 patients with NIHSS sores 0–5 (disabling or nondisabling symptoms) who were given tenecteplase 0.1

or 0.25 mg/kg for acute ischaemic stroke due to any proven and relevant intracranial occlusion.[117] The TEMPO-2 trial (NCT02398656) is an ongoing RCT that compares tenecteplase with standard care in a similar population.

Additional information

Recommendations for management of patients with large artery occlusions are also provided in the European Guidelines for mechanical thrombectomy.[14] Trials are underway to test the effectiveness of thrombectomy in patients with largeartery occlusion and NIHSS scores 0–5 (In Extremis/ Minor Stroke Therapy Evaluation [MOSTE; NCT 03796468], Endovascular Therapy for low NIHSS Ischemic Strokes [ENDOLOW; NCT 04167527]). In addition, two recent multicentre observational studies suggest a potential beneficial effect of IVT[118] and bridging therapy[119] in acute ischaemic stroke patients with minor stroke (NIHSS-scores<6) and large vessel occlusion.

Consensus recommendation

Expert consensus statement

For patients with acute minor, non-disabling ischaemic stroke of <4.5 h duration, and with large-vessel occlusion, 6 of 8 group members suggest intravenous thrombolysis with alteplase.

Practical Info

One group member (WW) did not vote or comment on this chapter because he has been involved in the data monitoring committee of a trial related to this topic (TEMPO-2).

For patients with acute ischaemic stroke of <4.5 h duration, and rapidly improving neurological signs, which are still disabling, there is insufficient evidence to make a recommendation. Please see the Expert consensus statement below.

Quality of evidence: Very low

Rationale

PICO 9.4 In patients with acute ischaemic stroke of <4.5 h duration, and with rapidly improving neurological signs, does IVT with

alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

We found no evidence of direct relevance for this question. The literature search did not identify any RCT of IVT in patients with rapidly improving symptoms, although the PRISMS trial included about 5% of such patients.[114] One large observational study of 29,200 patients with mild or rapidly improving symptoms, who did not receive IVT, showed that unfavourable outcomes were common (28.3% were not discharged to home, and 28.5% were unable to ambulate without assistance at hospital discharge), and strongly associated with baseline NIHSS score.[120]

Additional information

Rapidly improving stroke symptoms were a contraindication in the NINDS trial.[17] The original intent was to avoid inclusion of transient ischaemic attack (TIA) patients, who recover completely without treatment.[121] A working group of investigators from the pivotal NINDS trial that reviewed this exclusion criterion concluded that patients with improvement of any degree, but with a persisting neurological deficit that is potentially disabling, should be treated with alteplase.[121] The authors performed structured interviews of the original NINDS clinical trialists to form this conclusion.

Consensus recommendation

Expert consensus statement

For patients with acute ischaemic stroke of <4.5 h duration, and rapidly improving neurological signs, which are still disabling, 8 of 9 group members suggest intravenous thrombolysis with alteplase. The group agreed that the treatment decision should be based on the clinical status at presentation, and that it is not justifiable to wait for resolution of symptoms.

8.10 - Severe stroke

Strong recommendation

For patients with clinically severe acute ischaemic stroke of <4.5 h duration, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate ⊕⊕⊕

Rationale

PICO 10.1 In patients with severe acute ischaemic stroke of <4.5 h duration, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Severe stroke can be defined clinically (e.g. NIHSS score >25), or with CT or other brain imaging prior to IVT, e.g. visible infarction in more than 1/3 of the middle cerebral artery territory or an Alberta Stroke Program Early CT Score (ASPECTS) of <7.[122]

Clinically severe stroke. A study-level meta-analysis classified RCTs recruiting patient with 'more severe stroke' as trials with a case fatality of \geq 20% in the control group.[6] There was no evidence of heterogeneity in the effect of IVT with alteplase on death or disability between trials with different levels of average stroke severity, but this study did not use the threshold of NIHSS score 25 to define severe stroke. In the individual participant data meta-analysis by Emberson et al,[8] there was no clear evidence of heterogeneity in the effect of alteplase on excellent outcome (mRS 0–1) between groups of patients with different baseline NIHSS scores, after controlling for age and time to treatment (p for interaction=0.06). In the 622 participants with the

highest level of stroke severity (NIHSS score ≥22) alteplase improved the odds of excellent outcome (OR 3.25, 95% CI: 1.42–7.47; Table 8).[8] Regarding for better functional outcome), there was no evidence of an interaction (P for interaction=0.72) between higher NIHSS score and lesser benefit from alteplase.[26]

In IST-3, where the subgroup of patients with NIHSS score \geq 25 was reported specifically, there was evidence of an interaction (P=0.003) between stroke severity and the effect alteplase on good outcome (mRS score 0-2), with greater relative benefit in patients with more severe stroke. In the small subgroup of 146 patients with the most severe strokes (NIHSS scores \geq 25) alteplase-treated patients were non-significantly more likely to have a good outcome than patients in the control group (OR 7.43, 95% CI: 0.43-129.0).[9]

The individual participant data meta-analysis showed that the absolute risk of fatal ICH due to IVT with alteplase was highest in those participants with the highest stroke severity (NIHSS scores ≥22, 6.8% vs 0.6%; Table 8),[8] although the odds of fatal ICH with alteplase was similar in patients with high or low stroke severity. Altogether, these studies do not provide evidence that patients with the highest level of stroke severity have a lesser proportional benefit from alteplase.

Additional information

The European Medicine Agency stipulates in the product insert for Actilyse that 'Patients with severe stroke (as assessed clinically [NIHSS score >25] and/or by appropriate imaging techniques) . . . at baseline should not be treated with Actilyse' because 'patients with very severe stroke are at higher risk for intracerebral haemorrhage and death'.

Clinical Question/ PICO

Population: Patients with clinically severe acute ischaemic stroke of < 4.5 h duration

Intervention: IVT with alteplase

Comparator: No IVT

Outcome Timeframe	Study results and measurements	Absolute effect estimates No IVT IVT with alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
mRS 0-1 three months	Odds Ratio 3.25 (CI 95% 1.42 - 7.47) Based on data from 622 patients in 9 studies. (Randomized controlled)	26 80 per 1000 per 1000 Difference: 53 more per 1000 (CI 95% 10 more - 138 more)	Moderate Due to serious risk of bias, Due to serious indirectness, Upgraded due to strong association	IVT with alteplase probably increases excellent outcome (mRS score 0–1) compared to no IVT.
Fatal ICH seven days	Odds Ratio 10.94 (CI 95% 2.54 - 47.15) Based on data from 622 patients in 9 studies. (Randomized controlled)	6 62 per 1000 per 1000 Difference: 59 more per 1000 (CI 95% 10 more - 226 more)	Moderate Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision, Upgraded due to very strong association ²	IVT with alteplase probably increases risk of fatal ICH compared to no IVT.

1. Risk of bias: Serious. Although the 9 RCTs included in the individual patient data meta-analysis had patients with NIHSS

- 22, in many trials, patients with clinically very severe stroke (e.g. NIHSS >25 in ECASS-3) or radiologically severe stroke (e.g. attenuation of >1/3 of the MCA in ECASS 2 and ATLANTIS B) were excluded. Therefore, a selection bias is likely: patients with clinically severe stroke were not indiscriminately randomized in those trials.. **Inconsistency: No serious. Indirectness:**Serious. This result is based on an independent patient data meta-analysis of subgroups of 9 trials, and was restricted to patients with NIHSS 22. It is uncertain whether those results would also apply to patients with very severe stroke (e.g., NIHSS >25 or coma).. **Imprecision: No serious. Publication bias: No serious. Upgrade: Large magnitude of effect.** strong association.
- 2. **Risk of bias: Serious.** aAlthough the 9 RCTs included in the individual patient data meta-analysis had patients with NIHSS 22, in many trials, patients with clinically very severe stroke (e.g. NIHSS >25 in ECASS-3) or radiologically severe stroke (e.g. attenuation of >1/3 of the MCA in ECASS 2 and ATLANTIS B) were excluded. Therefore, a selection bias is likely: patients with clinically severe stroke were not indiscriminately randomized in those trials.. **Inconsistency: No serious. Indirectness: Serious.** This result is based on an independent patient data meta-analysis of subgroups of 9 trials, and was restricted to patients with NIHSS 22. It is uncertain whether those results would also apply to patients with very severe stroke (e.g., NIHSS >25 or coma).. **Imprecision: Serious.** The confidence interval is very wide. **Publication bias: No serious. Upgrade: Very large magnitude of effect.** very strong association.

Weak recommendation

For patients with acute ischaemic stroke of < 4.5 h duration, and with severe stroke, defined by the extent of early ischaemic changes on CT, we suggest that intravenous thrombolysis with alteplase be considered in selected cases (see the Expert consensus statement below).

Quality of evidence: Very Low

Rationale

PICO 10.1 In patients with severe acute ischaemic stroke of <4.5 h duration, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Severe stroke can be defined clinically (e.g. NIHSS score >25), or with CT or other brain imaging prior to IVT, e.g. visible infarction in more than 1/3 of the middle cerebral artery territory or an Alberta Stroke Program Early CT Score (ASPECTS) of <7.[122]

Extensive ischaemic change on baseline imaging. Studies have also used brain imaging to define severe stroke. A Cochrane review did not demonstrate any important statistical difference between the effect of alteplase in those with more and in those with less extensive ischaemic change on baseline CT scan.[6] We found no individual participant data meta-analysis of baseline brain imaging findings in patients in the large trials of alteplase. Although the presence of a greater degree of low attenuation on brain CT is associated with a much poorer outcome after ischaemic stroke,[123][124] there is no evidence that patients with larger lesion or with more tissue attenuation benefit less from alteplase in analyses from 3 individual trials, after adjustment for time to randomisation.[100][125][126] However, there is no trial specifically addressing this question, and extensive baseline ischemia was an exclusion criteria in the major IVT trials.

We have conducted a study-level meta-analysis of 3 trials in which inclusion of patients in spite of an early ischemic change of more than 1/3 of the middle cerebral artery territory was permitted (IST-3, NINDS and ECASS I).[100][125][127] The unadjusted pooled ORs for 'favourable' outcome (mRS 0–1 at three months in NINDS and ECASS I, Oxford Handicap Score 0–2 at six months) were 1.65 (0.38–7.20) and 1.55 (1.05–2.28) in patients with and without early ischemic change of more than 1/3 of the middle cerebral artery territory (Figure 9). We found no evidence that the

presence of an early ischemic change of more than 1/3 of middle cerebral artery territory significantly modifies the effect of IVT on favourable outcome (P for interaction=0.67). However, we observed a significant interaction of the presence of early ischemic changes on baseline CT on the association of IVT with three-month mortality (P for interaction=0.005). Patients treated with alteplase were at higher odds of three-month mortality compared with patients not treated with IVT (OR 3.90, 95% CI: 1.42–10.68; Figure 10).

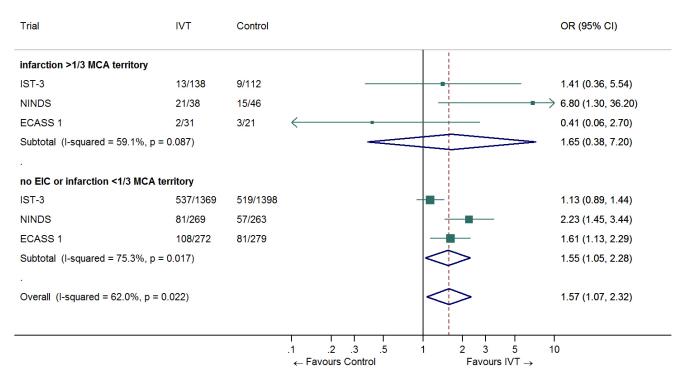


Figure 9. Pooled odds ratio for favourable outcome* in patients with ischaemic stroke of <4.5 h duration randomised to with IVT vs. control, stratified by the extent of early ischaemic change on baseline CT (> 1/3 vs.<1/3 of middle cerebral artery territory). Random effects meta-analysis, based on data from von Kummer et al., Patel et al. and IST-3 subgroup analyses.
*Favourable outcome at 3–6 months refers here to Oxford Handicap Scale 0–2 at six months in IST-3 and mRS 0–1 at three months in NINDS and ECASS 1. EIC denotes early ischaemic changes on baseline CT scan. There was no significant interaction between the extent of early ischemic changes (> 1/3 vs.<1/3 of the MCA territory) and the effect of IVT on favourable outcome (P for interaction = 0.67).

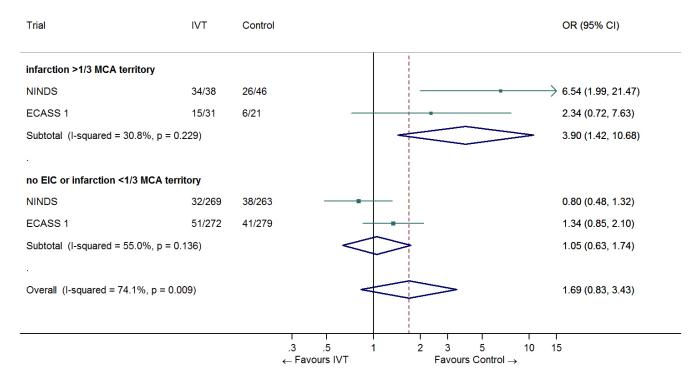


Figure 10. Pooled odds ratio for death at three months in patients with ischaemic stroke of<4.5 h duration randomised to IVT vs. control, stratified by the extent of early ischaemic change on baseline CT (> 1/3 vs.<1/3 of middle cerebral artery territory). Random effects meta-analysis, based on data from von Kummer et al. and Patel et al. EIC denotes early ischaemic changes on baseline CT scan. There was a significant interaction between the extent of early ischemic changes (> 1/3 vs.<1/3 of the MCA territory) and the effect of IVT on death at three months (P for interaction = 0.005).

An ASPECTS of <7 has also been used to define severe stroke.[128]

The recommendation for patients with clinically severe acute ischaemic stroke is based on meta-analyses of a number of RCTs. The quality of the evidence is moderate (Table 8). For severe stroke defined by the extent of ischaemic change on CT the recommendation is based on fewer data from fewer trials. The quality of the evidence is rated as very low (see Table 9 for details).

Clinical Question/ PICO

Population: Extensive ischaemic change on baseline imaging

Intervention: IVT with alteplase

Comparator: No IVT

Outcome Timeframe	Study results and measurements	Absolute e No IVT	effect estimates IVT with alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
Favourable outcome: mRS 0-1 at threemonths in	Odds Ratio 1.65 (CI 95% 0.38 - 7.2) Based on data from 386 patients in 3 studies. (Randomized controlled)	151 per 1000 Difference: 7	227 per 1000 6 more per 1000	Very Low Due to serious risk of bias, Due to serious inconsistency,	We are very uncertain of the effect of IVT with alteplase on mRS 0-1 at threemonths in ECASS-1 & NINDS and OHS 0-2

Outcome Timeframe	Study results and measurements	Absolute effect estimates No IVT IVT with alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
ECASS-1 & NINDS; OHS 0-2 at six months in IST-3		(CI 95% 88 fewer - 410 more)	Due to serious indirectness, Due to serious imprecision, Due to serious publication bias ¹	at six months in IST-3 compared to no IVT.
sICH	Odds Ratio 3.24 (CI 95% 0.72 - 14.6) Based on data from 250 patients in 1 studies. (Randomized controlled)	36 108 per 1000 per 1000 Difference: 71 more per 1000 (CI 95% 10 fewer - 315 more)	Very Low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision ²	We are very uncertain of the effect of IVT with alteplase on risk of sICH compared to no IVT.
Death three months	Odds Ratio 3.9 (CI 95% 1.42 - 10.68) Based on data from 146 patients in 2 studies. (Randomized controlled)	478 781 per 1000 per 1000 Difference: 303 more per 1000 (CI 95% 87 more - 429 more)	Moderate Due to serious risk of bias, Due to serious indirectness, Upgraded due to strong association other consideration ³	IVT with alteplase probably increases risk of death compared to no IVT.

- 1. **Risk of bias: Serious.** Selection bias: it is plausible that all patients with very extensive signs of brain infarction on baseline imaging were not systematically randomized. Besides, because advanced imaging was not used, it is likely that the included population is heterogeneous, consisting of patients with and without residual salvageable (penumbral) tissue despite extensive infarction.. **Inconsistency: Serious.** A strong benefit of IVT was observed in the NINDS trial (OR for favourable outcome 6.8; 95% CI: 1.30–36.2), whereas a trend towards deleterious effect was observed in ECASS-1 (OR for favourable outcome 0.4; 95% CI: 0.10–2.70).. **Indirectness: Serious.** In IST-3 and ECASS-1, patients could be treated up to six hours after symptom onset. In IST-3, to our knowledge extent of early ischemic change was not specifically reported as less or more than 1/3 of the MCA territory but according to 4 categories, of which the authors considered 'large or very large' to correspond to more than 1/3 of the MCA territory.100 Conversely, in NINDS and ECASS-1, all baseline images were centrally reviewed and classified as less or more than 1/3 of the MCA territory.125. **Imprecision: Serious.** The confidence interval is wide. However, in our meta-analysis we found evidence that presence of early ischaemic changes >1/3 of the middle cerebral artery territory modifies the effect of IVT on mortality at three months (P for interaction 1/40.005).. **Publication bias: Serious.**
- 2. **Risk of bias:** Serious. Selection bias: it is plausible that all patients with very extensive signs of brain infarction on baseline imaging were not systematically randomized. Besides, because advanced imaging was not used, it is likely that the included population is heterogeneous, consisting of patients with and without residual salvageable (penumbral) tissue despite extensive infarction.. **Inconsistency: No serious. Indirectness: Serious.** In IST-3 and ECASS-1, patients could be treated up to six hours after symptom onset. In IST-3, to our knowledge extent of early ischemic change was not specifically reported as less or more than 1/3 of the MCA territory but according to 4 categories, of which the authors considered 'large or very large' to correspond to more than 1/3 of the MCA territory.100 Conversely, in NINDS and ECASS-1, all baseline images were centrally reviewed and classified as less or more than 1/3 of the MCA territory.125. **Imprecision: Serious.** The confidence interval is wide. However, in our meta-analysis we found evidence that presence of early ischaemic changes >1/

3 of the middle cerebral artery territory modifies the effect of IVT on mortality at three months (P for interaction 40.005).. **Publication bias: No serious.**

3. **Risk of bias: Serious.** Selection bias: it is plausible that all patients with very extensive signs of brain infarction on baseline imaging were not systematically randomized. Besides, because advanced imaging was not used, it is likely that the included population is heterogeneous, consisting of patients with and without residual salvageable (penumbral) tissue despite extensive infarction.. **Inconsistency: No serious. Indirectness: Serious.** In IST-3 and ECASS-1, patients could be treated up to six hours after symptom onset. In IST-3, to our knowledge extent of early ischemic change was not specifically reported as less or more than 1/3 of the MCA territory but according to 4 categories, of which the authors considered 'large or very large' to correspond to more than 1/3 of the MCA territory.100 Conversely, in NINDS and ECASS-1, all baseline images were centrally reviewed and classified as less or more than 1/3 of the MCA territory.125. **Imprecision: No serious.** The confidence interval is wide. However, in our meta-analysis we found evidence that presence of early ischaemic changes >1/3 of the middle cerebral artery territory modifies the effect of IVT on mortality at three months (P for interaction \(^{1}40.005). **Publication bias: No serious. Upgrade: Large magnitude of effect.** Regarding IST-3, we could not find published data on the raw numbers or ORs for the association between IVT and death at six months, stratified by the extend of early ischaemic changes..

Consensus recommendation

Expert consensus statement

Seven of nine group members voted for intravenous thrombolysis with alteplase in selected patients with severe stroke associated with extended radiological signs of infarction (e.g., early ischemic change of more than 1/3 of the middle cerebral artery territory or ASPECTS <7 on plain CT). Patient selection criteria might include eligibility for an alternative reperfusion strategy (mechanical thrombectomy), results of advanced imaging (notably core/perfusion mismatch), time since symptom onset, extent of white matter lesions, other contraindications for IVT, and pre-stroke disability.

8.11 - High blood pressure and high blood glucose level

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, and with persistently increased systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg even after blood pressure lowering treatment, we suggest no intravenous thrombolysis.

Quality of evidence: Very low

Rationale

PICO 11.1 In patients with acute ischaemic stroke of <4.5 h duration, and with persistently increased blood pressure above 185/110 mmHg, even after blood pressure lowering treatment, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Increased blood pressure is a common finding during the first hours of ischaemic stroke, and may be considered an adaptive physiological response aiming to improve cerebral perfusion. However, increased blood pressure may also increase the risk of sICH after IVT. The majority of the RCTs of IVT with alteplase therefore excluded patients with systolic blood pressure >185mmHg or diastolic blood pressure >110 mmHg, and aimed to

maintain blood pressure below these values during the first 24 h.

In IST-3, an analysis by subgroups of baseline systolic (< 143, 144–164, >164mmHg) or diastolic blood pressure did not show a modification in the effect of alteplase on sICH, death at seven days, or functional outcome at six months.[129] However, results for patients with systolic blood pressure >185mmHg have not been published.

While analyses of RCTs have not shown an effect modification of IVT by high blood pressure, a number of analyses of observational data have shown that high blood pressure is associated with poorer prognosis. In patients treated with alteplase in the ECASS-2 trial, higher baseline, maximum, mean (per 10mmHg increase), and variability of systolic blood pressure were all inversely associated with excellent outcome (mRS score 0-1) at three months (OR 0.84, 95% CI: 0.74-0.94; OR=0.82, 95% CI: 0.73-0.91; OR=0.81, 95% CI: 0.71-0.93; OR 0.57, 95% CI: 0.35-0.92, respectively) and associated with an increased risk of parenchymal haemorrhage within the first seven days (OR 1.27, 95% CI: 1.07-1.51; OR 1.49, 95% CI: 1.27-1.75; OR 1.52, 95% CI: 1.23-1.87; OR 2.62, 95% CI: 1.40-4.87, respectively) after adjusting for age, sex, time from stroke onset to treatment, stroke severity, history of hypertension, medication with aspirin and the extent of hypodensity on initial CT.[130] Likewise, in an analysis of observational data from IST-3, the odds of sICH increased by 10% (95% Cl: 2-19) for each 10mmHg increase in baseline systolic blood pressure, after adjustment for baseline stroke severity.[131] In addition, a single-centre observational study reported that pretreatment blood pressure limit violations (systolic blood pressure >185mmHg and/or diastolic blood pressure>110mmHg) occurred frequently (12%) in everyday clinical practice and were independently associated with higher likelihood of sICH (OR 2.59, 95% CI: 1.07-6.25).[132] Also, in a recent retrospective analysis of the Safe Implementation of Treatments in Stroke (SITS) thrombolysis registry with regard to 11 off-label criteria according to the European licence for alteplase, elevated pretreatment blood pressure levels represented the only off-label criterion thatwas independently associated with a higher odds of sICH (OR 1.39; 95% CI: 1.08-1.80).[133]

A systematic review and meta-analysis of observational data from 56,513 patients found that higher pretreatment systolic blood pressure (OR 1.08, 95% CI: 1.01–1.16 per 10mm Hg increase, I2=82%) and higher post-treatment systolic blood pressure (OR 1.13 95% CI: 1.01–1.25 per 10mm Hg increase, I2=63%) were associated with an increased risk of sICH.[134] Higher systolic blood pressure was also associated with lower odds of good outcome (mRS 0–2) at three months: OR 0.91, 95% CI: 0.84–0.98 per 10mmHg increase in pretreatment pressure, I2=29%, and OR 0.70, 95% CI: 0.57–0.87 per 10mm Hg increase in post-treatment pressure, I2=0%).

Additional information

It should be noted that, based on current acute antihypertensive treatment options, persistent elevated blood pressure of >185/110 excluding patients from treatment is uncommon. There is evidence suggesting that it is also important to monitor blood pressure after treatment with alteplase. In a cohort of 1868 patients treated with alteplase, patients with sICH had significantly higher systolic blood pressure at several time-points after IVT compared with those without sICH (P<0.01 at 2 and 4 h; P<0.05 at 12 and 48 h). The odds ratios for development of sICH per 10mmHg increase in blood pressure at 2, 4, 12 and 48 h were 1.14 (95% CI: 1.03–1.25), 1.14 (95% CI: 1.03–1.25), 1.12 (95% CI: 1.01–1.23) and 1.12 (95% CI: 1.01–1.23), respectively.[135]

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg, which has subsequently been lowered to <185 and <110 mmHg, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

Rationale

PICO 11.2 In patients with acute ischaemic stroke of <4.5 h duration, and with increased blood pressure above 185/110mm Hg, which has subsequently been lowered to below 185/110mm Hg, does IVT with alteplase lead to better functional outcome than no

IVT?

Analysis of current evidence.

Blood pressure lowering treatment to values below 185/110mmHg was allowed in all completed RCTs of IVT with alteplase versus control, and so the results of these trials apply to these patients.

In the ENCHANTED trial, 2196 patients with systolic blood pressure >150mmHg and<185/110mmHg who were eligible for IVT with alteplase were randomised to intensive blood pressure lowering (target systolic blood pressure 130–140mm Hg within 1 h) or to a target systolic blood pressure<180mm Hg, and to keep blood pressure in that range over 72 h.[136] Mean systolic blood pressure over 24h was 144±10mmHg in the intensive group and 150±12mmHg in the control group. Functional outcome at 90 days did not differ between groups (unadjusted cOR for better functional outcome 1.01, 95% CI: 0.87–1.17, P=0.87). Fewer patients in the intensive group (14.8%) than in the control group (18.7%) had any ICH (OR 0.75, 0.60–0.94, P=0.01). Blood pressure reduction was also related to a non-significant decrease in type 2 parenchymal haemorrhage (OR 0.71, 95% CI: 0.50–1.01).

An analysis of observational data from IST-3 indicated that the use of blood pressure lowering treatment during the first 24 h were associated with a reduced risk of poor outcome (Oxford handicap scale 3–6) at six months (OR 0.78, 95% CI: 0.65–0.93, P=0.007), irrespective of whether the patient was given alteplase or not (p for interaction>0.05).131 However, analyses of the effect of blood pressure lowering treatment using observational data from the NINDS trial did not provide conclusive results.[137]

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with known pre-stroke hypertension, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate ⊕⊕⊕

Rationale

PICO 11.3 In patients with acute ischaemic stroke of <4.5 h duration, and with known pre-stroke hypertension, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Only two of the RCTs (ECASS-3 and IST-3) that were included in the individual participant data meta-analysis8 presented the effect of IVT with alteplase for patients with or without known pre-stroke hypertension. There was no evidence that known hypertension modifies the effect of IVT with alteplase on excellent outcome in ECASS-3 (P for interaction=0.19), or better functional outcome at six months in IST-3 (P for interaction=0.79).[129][138] There was also no evidence that known hypertension modifies the effect of IVT with alteplase on mortality or sICH in these two trials.

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with blood glucose levels above 22.2 mmol/L (400 mg/dL), we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Very Low

Intravenous thrombolysis should not prevent the administration of insulin therapy in acute ischaemic stroke patients with high blood glucose levels.[144]

Rationale

PICO 11.4 In patients with acute ischaemic stroke of <4.5 h duration, and with blood glucose level above >22.2 mmol/L (>400 mg/dL), does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Hyperglycaemia in the acute phase may represent stress, underlying impaired glucose tolerance or unrecognised diabetes mellitus. Higher blood glucose level at admission has been consistently associated with poorer functional outcome and sICH in acute ischemic stroke patients treated with or without IVT.[139][140] However, blood glucose level was not a modifier of the effect of alteplase on functional outcome in RCTs.9,129 It is uncertain whether this also holds true for patients with very high blood glucose levels (>22.2 mmol/L, >400 mg/dL) because they were not included in RCTs, owing to concerns of an increased risk of sICH,122 but also because hyperglycaemia can present with focal neurological deficits that mimic acute stroke.[141]

We identified only one observational study allowing the comparison of IVT and no IVT in acute ischaemic stroke patients with blood glucose levels >22.2 mmol/L. In this analysis of 9613 patients from the Virtual International Stroke Trials Registry (VISTA), only 23 patients had blood glucose levels >22.2 mmol/L. Of these, 6 had been treated with alteplase, and in this very small group no cases of sICH were observed.142 Compared with patients not treated with IVT, those who received IVT had a cOR for better functional outcome of 1.06 (95% CI: 0.19–5.91) and an OR for excellent functional outcome of 1.31 (0.08–20.61).

Large observational registries of patients treated with IVT provide some insight on the risk of sICH in patients with very high blood glucose levels. Out of 56,258 patients treated with IVT in the SITS registry, baseline blood glucose levels >22.2 mmol/L were documented in 91 patients and independently associated with a higher risk of sICH according to ECASS-2 criteria (OR 1.99, 95% CI: 1.01–3.92).[133] The incidence rate of sICH was 9.9% (95% CI: 5.3%–17.7%) and 3.3% (95% CI: 1.1–9.4%) according to the ECASS-2 and SITS definitions, respectively.

Of note, persistent hyperglycemia may be a more important predictor of poor functional outcome than baseline hyperglycemia in patients with acute ischaemic stroke.[143]

Given the lack of evidence of an heterogeneity in the effect of alteplase in patients with higher blood glucose levels, and the available data regarding the risk of sICH in patients with glucose level >22.2 mmol/L, we believe that alteplase should not be withheld in these patients, even though they have a substantial risk of poor functional outcome.

Additional information

In an analysis of 16,049 patients treated with alteplase and included in the SITS registry,[145] blood glucose as a continuous variable was independently associated with a higher case fatality (p<0.001), poorer functional outcome (p<0.001) and increased risk of sICH (P=0.005). Compared to patients with blood glucose level 80–120 mg/dL, patients with blood glucose from 181 to 200 mg/dL had an increased risk of sICH (OR 2.86, 95% CI: 1.69–4.83, p<0.001). The associations between blood glucose and outcomes were similar in patients with or without diabetes mellitus, except for case fatality (p for interaction<0.001) and sICH (p for interaction=0.02), for which the associations were not statistically significant in patients with diabetes mellitus.

In the SITS-EAST registry, 14 of 5461 patients (0.3%) had blood glucose levels >22.2 mmol/L, and these patients had an increased rate of sICH (unadjusted OR 5.91, 95% CI: 1.18–12.5, P=0.03) and unfavourable functional outcome (adjusted OR 8.59, 95% CI: 0.88–83.9 P=0.06).[146]

Intravenous thrombolysis should not prevent the administration of insulin therapy in acute ischaemic stroke patients with high blood glucose levels. More information about management of hyperglycaemia in patients with acute ischaemic stroke can be found in the ESO guideline on glycaemia management in acute stroke.[144]

The Stroke Hyperglycemia Insulin Network Effort (SHINE) randomized clinical trial included adult patients with hyperglycemia (glucose concentration of >110 mg/dL in case of diabetes or \geq 150 mg/dL in patients without diabetes) and acute ischemic stroke who were enrolled within 12 h from stroke onset.[147] Patients were randomized to receive continuous intravenous insulin (target blood glucose concentration of 80–130 mg/dL, intensive treatment group: n=581) or subcutaneous insulin (target blood glucose concentration of 80–179 mg/d, standard treatment group: n=570) for up to 72 h. A total of 725 enrolled patients (63%) received IVT. The proportion of patients with favourable outcome at 90 days did not differ in the two arms of the trial (20.5% vs. 21.6%) and in the subgroup of patients receiving IVT (23.0% vs. 24.9%). The number of patients who received blood glucose lowering therapy prior to alteplase bolus was not reported.

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with known diabetes mellitus, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate +++

Rationale

PICO 11.5 In patients with acute ischaemic stroke of <4.5 h duration, and with known diabetes mellitus, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Only two of the RCTs (ECASS-3 and IST-3) that were included in the individual participant data meta-analysis[8] presented the effect of IVT with alteplase for patients with or without known diabetes mellitus. There was no evidence that known diabetes mellitus modified the effect of IVT with alteplase on excellent outcome in ECASS-3 (P for interaction=0.17), or better functional outcome at six months in IST-3 (P for interaction=0.91).[129][138] There was also no evidence that known diabetes mellitus modified the effect of IVT with alteplase on mortality or sICH in these two trials. Amongst 54,206 acute ischemic stroke patients included in the SITS registry and treated with IVT, there was no interaction of the history of diabetes mellitus on the association of admission hyperglycemia (≥144 mg/dL) with sICH according to the SITS definition (P for interaction=0.27), three-month good functional outcome (P for interaction

=0.92) and three-month mortality (P for interaction=0.63).[148]

8.12 - Use of antithrombotic drugs before the stroke

PICO 12.3 In patients with acute ischaemic stroke of <4.5 h duration, who use NOACs, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

The use of non-VKA oral anticoagulants (NOACs, i.e. direct thrombin inhibitors and factor Xa inhibitors) may increase the risk of sICH after IVT with alteplase, and alteplase is contraindicated if NOAC has been used during the last 48 h before stroke onset, according to the labels for these drugs.

In an observational study of 51 patients taking DOACs and 390 patients treated with VKA, sICH after intravenous alteplase occurred in 4.0% of patients taking NOACs and 3.6% of patients taking VKA (no significant difference).[169] Out of 42,887 patients treated with alteplase in the Get With The Guidelines Registry, 251 (0.6%) were treated with NOACs and 1,500 (3.5%) with warfarin.[170] Compared with patients without anticoagulants, the adjusted OR for sICH was 0.92 (95% CI: 0.51–1.65) for those on NOACs and 0.85 (95% CI: 0.66–1.10) for those on warfarin. There were also no significant differences across the three groups in the risk for serious systemic haemorrhage or in-hospital deaths.

A recent meta-analysis of cohort studies reported no additional risk of sICH following IVT among selected patients taking NOACs within 48 h compared to patients treated with warfarin (ECASS-2 criteria: OR 0.77, 95% CI: 0.28–2.16) and compared to patients without anticoagulation pretreatment (OR, 0.87, 95% CI: 0.32–2.41).[171] Patient selection was based on various coagulation assays.

A number of decision algorithms have been proposed to identify patients treated with NOACs who can be given IVT.[165][172][173][174][175] According to these algorithms, thrombolytic treatment can be given (i) in patients using dabigatran if thrombin time is normal[172] or below 60 seconds,[173] (ii) in patients using rivaroxaban if the drug plasma level is<20 ng/ml[174] or<50 ng/ml,[173] or if anti-Xa activity is<0.5 U/ml,[173] (iii) in patients using apixaban if anti-Xa activity is<0.5 U/ml,[173] (iv) in patients using edoxaban if anti-Xa activity<0.5 U/ml,[173] The safety of these treatment decision algorithms has not been tested in clinical practice, with the exception of the cut-off plasma level of rivaroxaban (<20ng/ml).[174] The coagulation parameters used to select patients for IVT in these studies were different, and global coagulation tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and INR are not specific for NOACs. Further research is therefore needed to identify the optimal coagulation parameters (e.g. thrombin time

for dabigatran, direct factor Xa activity for rivaroxaban, apixaban and edoxaban, or individual NOAC plasma levels). Until such data are available, we believe that IVT with alteplase should not be used indiscriminately in patients who have received a NOAC dose within the last 48 h in patients with normal renal function.

Others have proposed the use of agents to reverse the anticoagulant effects of NOACs.[172][173][174] For example, idarucizumab has been used to reverse dabigatran activity before alteplase treatment, and this treatment algorithm has been tested in small studies in the prehospital and hospital settings.[176][177][178] However, there are theoretical concerns that idarucizumab may potentiate the prothrombotic activity in the acute phase of ischaemic stroke, and increase the risk of ischaemic events.[172] Nevertheless, such complications were not documented in two national cohorts from Germany and New Zealand reporting the experience of IVT for acute ischaemic stroke patients pretreated with idarucizumab for dabigatran reversal.[177][179]

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, who used single or dual antiplatelet agents prior to the stroke, we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

Rationale

PICO 12.1 In patients with acute ischaemic stroke of <4.5 h duration, who use antiplatelet agents, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Treatment with antiplatelet agents before an ischaemic stroke may increase the risk of sICH in patients given alteplase,[149] but antiplatelet treatment was not an exclusion criterion in the completed RCTs. Some of those trials have analysed separately patients who used an antiplatelet agent before stroke onset. A secondary analysis of IST-3 showed that the proportion of sICH in patients treated with antiplatelet therapy within the previous 48 h

before stroke onset was 9% for those allocated alteplase versus 1% in control, compared with 5% for alteplase and 1% control for those with no recent antiplatelet therapy (P=0.019 for interaction).[129] A secondary analysis of the ENCHANTED trial indicated an association between standard-dose alteplase and risk of sICH in patients receiving antiplatelets before the

stroke,[62] but antiplatelet pre-treatment was not associated with worse functional outcome after adjustment for potential confounders.[63]

Meta-analyses of observational data from RCTs or from a combination of RCTs and observational studies indicated that antiplatelet agents increased the risk of sICH in unadjusted analyses (absolute increase 6.5%, 95% CI: 5.8–7.6%),[63] but not after adjustment for confounders.[150][151][152] Another analysis of observational data, from VISTA, indicated that alteplase compared to no alteplase improved functional outcome in patients who had received pre-treatment with a single antiplatelet agent (common OR 1.42, 95% CI: 1.19–1.70).[142]

The literature search identified no RCT of IVT in patients using dual antiplatelet therapy (DAPT) before the stroke. The VISTA analysis showed a relatively high risk of sICH in patients receiving DAPT (8.5%, 95% CI: 3.9–17.2%), but the analysis was unadjusted and the increase in sICH was statistically non-significant.[142] Similarly, an analysis of patients given IVT within the Stroke–Acute Ischemic–NXY Treatment (SAINT) I and II trials indicated that DAPT was associated with a higher risk of sICH but not with a higher risk of poor functional outcome (mRS score 3–6) at threemonths.[153]

Other studies have used propensity score matching to attempt to account for imbalances between patients with and without DAPT. These studies indicate that patients who use DAPT before IVT with alteplase have comparable sICH rates and comparable functional outcome and survival at threemonths compared with patients who don't use antiplatelet drugs.[154][155]

Finally, a recent meta-analysis of 9 observational studies comprising 66,675 acute ischaemic stroke patients treated with IVT failed to document any association between DAPT and the likelihood of sICH, three-month good functional outcome (mRS 0-2), three-month excellent functional outcome (mRS 0-1), and three-month mortality in adjusted analyses controlling for potential confounders.[156]

In summary, analyses of observational data indicate that single or dual antiplatelet pre-treatment is not independently associated with poorer functional outcome and higher risk of sICH. Use of antiplatelet agents should therefore not be used as a reason to withhold IVT with alteplase in patients with acute ischaemic stroke, although more research is needed.

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists and have INR \leq 1.7 we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

Rationale

PICO 12.2 In patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Patients given vitamin K antagonists (VKA) and with International Normalized Ratio (INR) >1.7 were excluded from the RCTs of IVT, and the European license for alteplase precludes treatment in all patients taking VKA. In a systematic review and meta-analysis of observational studies,157 25 of 240 patients (10.4%) who used

VKA (median INR 1.14–1.5) experienced an sICH, compared with 184 of 3391 patients (5.4%) without VKA medication (OR 2.58, 95% CI: 1.13–5.89, P=0.02; I2=56%). However, VKA use was not associated with poor functional outcome (mRS ≥3, OR 1.18, 95% CI: 0.85–1.61, P=0.32; I2=15%) or death (OR 1.22, 95% CI: 0.85–1.75, P=0.28; I2=0%).

Among 45,074 patients from the SITS registry treated with alteplase, 768 (1.7%) used warfarin and had INR 1.7.158 After adjustment for potential confounders, warfarin use was not significantly associated with sICH (adjusted OR 1.26, 95% CI: 0.82−1.70), and no increase in poor functional outcome or death at three months was observed. Among 23,437 patients treated with alteplase in the U.S. Get With The Guidelines Registry, 1802 (7.7%) were treated with warfarin with an INR ≤1.7 (median

1.20; IQR 1.07–1.40). After adjustment for potential confounders, warfarin use was not significantly associated with sICH (adjusted OR 1.01, 95% CI: 0.82–1.25), serious systemic haemorrhage, or in-hospital death.[159]

In patients with INR \leq 1.7, other large registries[159][160][161] have also indicated that IVT with alteplase is associated with a low risk of sICH and poor outcomes, both in the 0–3 and in the 3–4.5 h time windows, although this may have been due to confounding.[160] Moreover, data from VISTA showed that alteplase was associated with improved functional outcome in patients given VKA and with INR \leq 1.7 (cOR for better functional outcome 2.20, 95% CI: 1.12–4.32; Table 10).[142]

There is little data on the rates of sICH in patients using VKA and INR >1.7, and the reported rates are highly variable (0% in 14 patients,[142] 3% in 33 patients[159] and 30% in 10 patients[162]).

Additional information

Case series indicate that prothrombin complex concentrates can be used to reverse the effect of VKAs in patients who are eligible for thrombolytic treatment and have INR >1.7.[163],[164] However, prothrombin complex concentrates might enhance coagulation, which can lead to a worsening of patients' neurological deficits.[165] Mechanical thrombectomy appears to be safe in patients with large vessel occlusion who have been pre-treated with a VKA and with INR >1.7.[166][167][168]

Clinical Question/ PICO

Population: Patients with acute ischaemic stroke of < 4.5 h duration who use vitamin K antagonists

Intervention: IVT with alteplase

Comparator: No IVT

Outcome Timeframe	Study results and measurements	Absolute effect estimates No IVT IVT with alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
Better functional outcome shift analysis of the mRS at threemonths	Odds Ratio 2.2 (CI 95% 1.12 - 4.32) Based on data from 157 patients in 1 studies. (Observational (non- randomized))	CI 95%	Low 1	
sICH	Odds Ratio Based on data from 157 patients in 1 studies. (Observational (nonrandomized))	CI 95%	Very Low Due to serious imprecision ²	
Death three months	Odds Ratio 0.68 (CI 95% 0.25 - 1.86) Based on data from patients in 1 studies. (Observational (non- randomized))	Difference: 1 fewer per 1000 (CI 95% 2 fewer - 0 fewer)	Low 3	

- 1. **Risk of bias: No serious.** An important risk of bias, notably of selection bias and confounding, exists in this pooled analysis based on RCTs of neuroprotectants. However, we consider that those limitations are already taken into account in mentioning in GRADEpro that this analysis corresponds to an observantional study and have therefore not further downgraded the quality of evidence.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
- 2. **Risk of bias: No serious.** An important risk of bias, notably of selection bias and confounding, exists in this pooled analysis based on RCTs of neuroprotectants. However, we consider that those limitations are already taken into account in mentioning in GRADEpro that this analysis corresponds to an observantional study and have therefore not further downgraded the quality of evidence.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Very few events.. **Publication bias: No serious.**
- 3. **Risk of bias: No serious.** An important risk of bias, notably of selection bias and confounding, exists in this pooled analysis based on RCTs of neuroprotectants. However, we consider that those limitations are already taken into account in mentioning in GRADEpro that this analysis corresponds to an observantional study and have therefore not further downgraded the quality of evidence.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists and have INR >1.7 we recommend no intravenous thrombolysis.

Quality of evidence: Very Low

Rationale

PICO 12.2 In patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

There is little data on the rates of sICH in patients using VKA and INR >1.7, and the reported rates are highly variable (0% in 14 patients,[142] 3% in 33 patients[159] and 30% in 10 patients[162]).

Additional information

Case series indicate that prothrombin complex concentrates can be used to reverse the effect of VKAs in patients who are eligible for thrombolytic treatment and have INR >1.7.[163],[164] However, prothrombin complex concentrates might enhance coagulation, which can lead to a worsening of patients' neurological deficits.[165] Mechanical thrombectomy appears to be safe in patients with large vessel occlusion who have been pre-treated with a VKA and with INR >1.7.[166][167][168]

Clinical Question/ PICO

Population: Patients with acute ischaemic stroke of < 4.5 h duration who use vitamin K antagonists

Intervention: IVT with alteplase

Comparator: No IVT

Outcome Timeframe	Study results and measurements	Absolute effect estimates No IVT IVT with alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
Better functional outcome shift analysis of the mRS at threemonths	Odds Ratio 2.2 (CI 95% 1.12 - 4.32) Based on data from 157 patients in 1 studies. (Observational (non- randomized))	CI 95%	Low 1	
sICH	Odds Ratio Based on data from 157 patients in 1 studies. (Observational (nonrandomized))	CI 95%	Very Low Due to serious imprecision ²	

Outcome Timeframe	Study results and measurements	Absolute effect estimates No IVT IVT with alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
Death three months	Odds Ratio 0.68 (CI 95% 0.25 - 1.86) Based on data from patients in 1 studies. (Observational (nonrandomized))	Difference: 1 fewer per 1000 (CI 95% 2 fewer - 0 fewer)	Low 3	

- 1. **Risk of bias: No serious.** An important risk of bias, notably of selection bias and confounding, exists in this pooled analysis based on RCTs of neuroprotectants. However, we consider that those limitations are already taken into account in mentioning in GRADEpro that this analysis corresponds to an observantional study and have therefore not further downgraded the quality of evidence.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
- 2. **Risk of bias:** No serious. An important risk of bias, notably of selection bias and confounding, exists in this pooled analysis based on RCTs of neuroprotectants. However, we consider that those limitations are already taken into account in mentioning in GRADEpro that this analysis corresponds to an observantional study and have therefore not further downgraded the quality of evidence.. **Inconsistency:** No serious. **Indirectness:** No serious. **Imprecision:** Serious. Very few events.. **Publication bias:** No serious.
- 3. **Risk of bias: No serious.** An important risk of bias, notably of selection bias and confounding, exists in this pooled analysis based on RCTs of neuroprotectants. However, we consider that those limitations are already taken into account in mentioning in GRADEpro that this analysis corresponds to an observantional study and have therefore not further downgraded the quality of evidence.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, who use vitamin K antagonists, and for whom the results of coagulation testing is unknown, we recommend no intravenous thrombolysis.

Quality of evidence: Very low

Rationale

PICO 12.2 In patients with acute ischaemic stroke of < 4.5 h duration, who use vitamin K antagonists, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

There is little data on the rates of sICH in patients using VKA and INR >1.7, and the reported rates are highly variable (0% in 14 patients,[142] 3% in 33 patients[159] and 30% in 10 patients[162]).

Additional information

Case series indicate that prothrombin complex concentrates can be used to reverse the effect of VKAs in patients who are eligible for thrombolytic treatment and have INR >1.7.[163],[164] However, prothrombin complex concentrates might enhance coagulation, which can lead to a worsening of patients' neurological deficits.[165] Mechanical thrombectomy appears

to be safe in patients with large vessel occlusion who have been pre-treated with a VKA and with INR >1.7.[166][167][168]

Clinical Question/ PICO

Population: Patients with acute ischaemic stroke of < 4.5 h duration who use vitamin K antagonists

Intervention: IVT with alteplase

Comparator: No IVT

Outcome Timeframe	Study results and measurements	Absolute effect estimates No IVT IVT with alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
Better functional outcome shift analysis of the mRS at threemonths	Odds Ratio 2.2 (CI 95% 1.12 - 4.32) Based on data from 157 patients in 1 studies. (Observational (non- randomized))	CI 95%	Low 1	
sICH	Odds Ratio Based on data from 157 patients in 1 studies. (Observational (nonrandomized))	CI 95%	Very Low Due to serious imprecision ²	
Death three months	Odds Ratio 0.68 (CI 95% 0.25 - 1.86) Based on data from patients in 1 studies. (Observational (non- randomized))	Difference: 1 fewer per 1000 (CI 95% 2 fewer - 0 fewer)	Low 3	

- 1. **Risk of bias: No serious.** An important risk of bias, notably of selection bias and confounding, exists in this pooled analysis based on RCTs of neuroprotectants. However, we consider that those limitations are already taken into account in mentioning in GRADEpro that this analysis corresponds to an observantional study and have therefore not further downgraded the quality of evidence.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
- 2. **Risk of bias: No serious.** An important risk of bias, notably of selection bias and confounding, exists in this pooled analysis based on RCTs of neuroprotectants. However, we consider that those limitations are already taken into account in mentioning in GRADEpro that this analysis corresponds to an observantional study and have therefore not further downgraded the quality of evidence.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Very few events.. **Publication bias: No serious.**
- 3. **Risk of bias: No serious.** An important risk of bias, notably of selection bias and confounding, exists in this pooled analysis based on RCTs of neuroprotectants. However, we consider that those limitations are already taken into account in mentioning in GRADEpro that this analysis corresponds to an observantional study and have therefore not further downgraded the quality of evidence.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and for whom there is no specific coagulation tests available (i.e. calibrated anti-Xa-activity for factor Xa inhibitors, thrombin time for dabigatran, or the NOAC blood concentrations), we suggest no intravenous thrombolysis.

Quality of evidence: Very Low

Rationale

PICO 12.3 In patients with acute ischaemic stroke of <4.5 h duration, who use NOACs, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

The use of non-VKA oral anticoagulants (NOACs, i.e. direct thrombin inhibitors and factor Xa inhibitors) may increase the risk of sICH after IVT with alteplase, and alteplase is contraindicated if NOAC has been used during the last 48 h before stroke onset, according to the labels for these drugs.

In an observational study of 51 patients taking DOACs and 390 patients treated with VKA, sICH after intravenous alteplase occurred in 4.0% of patients taking NOACs and 3.6% of patients taking VKA (no significant difference).[169] Out of 42,887 patients treated with alteplase in the Get With The Guidelines Registry, 251 (0.6%) were treated with NOACs and 1,500 (3.5%) with warfarin.[170] Compared with patients without anticoagulants, the adjusted OR for sICH was 0.92 (95% CI: 0.51–1.65) for those on NOACs and 0.85 (95% CI: 0.66–1.10) for those on warfarin. There were also no significant differences across the three groups in the risk for serious systemic haemorrhage or in-hospital deaths.

A recent meta-analysis of cohort studies reported no additional risk of sICH following IVT among selected patients taking NOACs within 48 h compared to patients treated with warfarin (ECASS-2 criteria: OR 0.77, 95% CI: 0.28–2.16) and compared to patients without anticoagulation pretreatment (OR, 0.87, 95% CI: 0.32–2.41).[171] Patient selection was based on various coagulation assays.

A number of decision algorithms have been proposed to identify patients treated with NOACs who can be given IVT.[165][172][173][174][175] According to these algorithms, thrombolytic treatment can be given (i) in patients using dabigatran if thrombin time is normal[172] or below 60 seconds,[173] (ii) in patients using rivaroxaban if the drug plasma level is<20 ng/ml[174] or<50 ng/ml,[173] or if anti-Xa activity is<0.5 U/ml,[173] (iii) in patients using apixaban if anti-Xa activity is<0.5 U/ml,[173] The safety of these treatment decision algorithms has not been tested in clinical practice, with the exception of the cut-off plasma level of rivaroxaban (<20ng/ml).[174] The coagulation parameters used to select patients for IVT in these studies were different, and global coagulation tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and INR are not specific for NOACs. Further research is therefore needed to identify the optimal coagulation parameters (e.g. thrombin time

for dabigatran, direct factor Xa activity for rivaroxaban, apixaban and edoxaban, or individual NOAC plasma levels). Until such data are available, we believe that IVT with alteplase should not be used indiscriminately in patients who have received a NOAC dose within the last 48 h in patients with normal renal function.

Others have proposed the use of agents to reverse the anticoagulant effects of NOACs.[172][173][174] For example, idarucizumab has been used to reverse dabigatran activity before alteplase treatment, and this treatment algorithm has been tested in small studies in the prehospital and hospital settings.[176][177][178] However, there are theoretical concerns that idarucizumab may potentiate the prothrombotic activity in the acute phase of ischaemic stroke, and increase the risk of ischaemic events.[172] Nevertheless, such complications were not documented in two national cohorts from Germany and New Zealand reporting the experience of IVT for acute ischaemic stroke patients pretreated with idarucizumab for dabigatran reversal.[177][179]

Additional information

Measurement of anti-Xa activity has been proposed to select acute ischaemic stroke patients pretreated with factor Xa inhibitors for IVT, particularly where NOAC drug levels are not readily available.[173] Of note, mechanical thrombectomy appears to be safe in patients with large vessel occlusion who have used a NOAC within last 48 h of symptom onset.[168][172][173][174][180]

Andexanet alfa is a modified recombinant factor Xa. It is catalytically inactive and cannot participate in coagulation, but it retains the ability to bind to and sequester factor Xa inhibitors. It has been conditionally approved by US FDA (Food and Drug Administration) in 2018 and European Medicines Agency in 2019 for the reversal of the anticoagulant effects of the Factor Xa inhibitors (apixaban or rivaroxaban) in patients experiencing uncontrolled or lifethreatening bleeding based on the results of the ANNEXA-4 study.[181] Andexanet alfa could reverse the anticoagulant effects of Factor Xa inhibitors in acute ischaemic stroke patients otherwise eligible for IVT who have been pretreated with apixaban or rivaroxaban.

However, there is only anecdotal published evidence about acute ischaemic stroke patients treated with IVT following rivaroxaban or apixaban reversal with andexanet alfa. Importantly, the infusion of andexanet alfa requires two hours, which may have implications for the eligibility of patients to receive alteplase with regard to the approved time window of 4.5 h.[182] Furthermore, a rebound effect of anti-Xa activity may occur. In contrast to idarucizumab in patients treated with dabigatran, andexanet alpha has not been approved for reversing Factor Xa inhibitor activity in patients who require emergency surgery/urgent procedures.[183][184] Besides, the cost of andexanet alfa, which has not been approved for edoxaban reversal,[184] is considerable.[182] Finally, a safety analysis conducted in the overall ANNEXA-4 study population has documented 40 thrombotic events (7 myocardial infarctions, 15 transient ischemic attacks or ischaemic strokes, 18 venous thromboembolic events) occurring in 34 (10%) patients at 30 days.[181] Eleven patients had a thromboembolic event within five days of receiving andexanet alfa and 8 patients had an event after restarting anticoagulation.[181] Therefore, the U.S. FDA prescribing information for andexanet alfa includes a black box warning regarding the risk of venous and arterial thromboembolic events.[185]

In summary, we caution against the off-label use of andexanet alfa for reversal of anticoagulant activity of apixaban or rivaroxaban in acute ischaemic stroke patients who are otherwise eligible for IVT.

For patients with acute ischaemic stroke of <4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and who have an anti-Xa activity <0.5 U/ml (for factor Xa inhibitors) or thrombin time <60 s (for direct thrombin inhibitors), there is insufficient evidence to make an evidence-based recommendation. Please see the Expert consensus statement below.

Quality of evidence: Very low \oplus

Rationale

Please click on 'Rationale' under the 'Expert Consensus Statement' section below.

For patients with acute ischaemic stroke of <4.5 h duration, who used dabigatran during the last 48 h before stroke onset, there is insufficient evidence to make a recommendation for or against the use of the combination of idarucizumab and intravenous thrombolysis with alteplase over no intravenous thrombolysis. Please see the Expert consensus statement below.

Quality of evidence: Very low

Rationale

Please click on 'Rationale' under the 'Expert Consensus Statement' section below.

Consensus recommendation

Expert consensus statement

For patients with acute ischaemic stroke of <4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and who have an anti-Xa activity <0.5U/ml (for factor Xa inhibitors) or thrombin time <60 s (for direct thrombin inhibitors) 7 of 9 group members suggest IVT with alteplase.

For patients with acute ischaemic stroke of <4.5 h duration, who used dabigatran during the last 48 h before stroke onset, 8 of 9 group members suggest the combination of idarucizumab and intravenous thrombolysis with alteplase over no intravenous thrombolysis.

For patients with acute ischaemic stroke of <4.5 h duration, who used factor Xa inhibitors during the last 48 h before stroke onset, 9 of 9 group members suggest against the combination of andexanet and intravenous thrombolysis with alteplase over no intravenous thrombolysis.

Rationale

PICO 12.3 In patients with acute ischaemic stroke of <4.5 h duration, who use NOACs, does IVT with alterplase lead to better functional outcome than no IVT?

Analysis of current evidence.

The use of non-VKA oral anticoagulants (NOACs, i.e. direct thrombin inhibitors and factor Xa inhibitors) may increase the risk of sICH after IVT with alteplase, and alteplase is contraindicated if NOAC has been used during the last 48 h before stroke onset, according to the labels for these drugs.

In an observational study of 51 patients taking DOACs and 390 patients treated with VKA, sICH after intravenous alteplase occurred in 4.0% of patients taking NOACs and 3.6% of patients taking VKA (no significant difference).[169] Out of 42,887 patients treated with alteplase in the Get With The Guidelines Registry, 251 (0.6%) were treated with NOACs and 1,500 (3.5%) with warfarin.[170] Compared with patients without anticoagulants, the adjusted OR for sICH was 0.92 (95% CI: 0.51–1.65) for those on NOACs and 0.85 (95% CI: 0.66–1.10) for those on warfarin. There were also no significant differences across the three groups in the risk for serious systemic haemorrhage or in-hospital deaths.

A recent meta-analysis of cohort studies reported no additional risk of sICH following IVT among selected patients taking NOACs within 48 h compared to patients treated with warfarin (ECASS-2 criteria: OR 0.77, 95% CI: 0.28–2.16) and compared to patients without anticoagulation pretreatment (OR, 0.87, 95% CI: 0.32–2.41).[171] Patient selection was based on various coagulation assays.

A number of decision algorithms have been proposed to identify patients treated with NOACs who can be given IVT.[165][172][173][174][175] According to these algorithms, thrombolytic treatment can be given (i) in patients using dabigatran if thrombin time is normal[172] or below 60 seconds,[173] (ii) in patients using rivaroxaban if the drug plasma level is<20 ng/ml[174] or<50 ng/ml,[173] or if anti-Xa activity is<0.5 U/ml,[173] (iii) in patients using apixaban if anti-Xa activity is<0.5 U/ml,[173] The safety of these treatment decision algorithms has not been tested in clinical practice, with the exception of the cut-off plasma level of rivaroxaban (<20ng/ml).[174] The coagulation parameters used to select patients for IVT in these studies were different, and global coagulation tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and INR are not specific for NOACs. Further research is therefore needed to identify the optimal coagulation parameters (e.g. thrombin time

for dabigatran, direct factor Xa activity for rivaroxaban, apixaban and edoxaban, or individual NOAC plasma levels). Until such data are available, we believe that IVT with alteplase should not be used indiscriminately in patients who have received a NOAC dose within the last 48 h in patients with normal renal function.

Others have proposed the use of agents to reverse the anticoagulant effects of NOACs.[172][173][174] For example, idarucizumab has been used to reverse dabigatran activity before alteplase treatment, and this treatment algorithm has been

tested in small studies in the prehospital and hospital settings.[176][177][178] However, there are theoretical concerns that idarucizumab may potentiate the prothrombotic activity in the acute phase of ischaemic stroke, and increase the risk of ischaemic events.[172] Nevertheless, such complications were not documented in two national cohorts from Germany and New Zealand reporting the experience of IVT for acute ischaemic stroke patients pretreated with idarucizumab for dabigatran reversal.[177][179]

Additional information

Measurement of anti-Xa activity has been proposed to select acute ischaemic stroke patients pretreated with factor Xa inhibitors for IVT, particularly where NOAC drug levels are not readily available.[173] Of note, mechanical thrombectomy appears to be safe in patients with large vessel occlusion who have used a NOAC within last 48 h of symptom onset.[168][172][173][174][180]

Andexanet alfa is a modified recombinant factor Xa. It is catalytically inactive and cannot participate in coagulation, but it retains the ability to bind to and sequester factor Xa inhibitors. It has been conditionally approved by US FDA (Food and Drug Administration) in 2018 and European Medicines Agency in 2019 for the reversal of the anticoagulant effects of the Factor Xa inhibitors (apixaban or rivaroxaban) in patients experiencing uncontrolled or lifethreatening bleeding based on the results of the ANNEXA-4 study.[181] Andexanet alfa could reverse the anticoagulant effects of Factor Xa inhibitors in acute ischaemic stroke patients otherwise eligible for IVT who have been pretreated with apixaban or rivaroxaban.

However, there is only anecdotal published evidence about acute ischaemic stroke patients treated with IVT following rivaroxaban or apixaban reversal with andexanet alfa. Importantly, the infusion of andexanet alfa requires two hours, which may have implications for the eligibility of patients to receive alteplase with regard to the approved time window of 4.5 h.[182] Furthermore, a rebound effect of anti-Xa activity may occur. In contrast to idarucizumab in patients treated with dabigatran, andexanet alpha has not been approved for reversing Factor Xa inhibitor activity in patients who require emergency surgery/urgent procedures.[183][184] Besides, the cost of andexanet alfa, which has not been approved for edoxaban reversal,[184] is considerable.[182] Finally, a safety analysis conducted in the overall ANNEXA-4 study population has documented 40 thrombotic events (7 myocardial infarctions, 15 transient ischemic attacks or ischaemic strokes, 18 venous thromboembolic events) occurring in 34 (10%) patients at 30 days.[181] Eleven patients had a thromboembolic event within five days of receiving andexanet alfa and 8 patients had an event after restarting anticoagulation.[181] Therefore, the U.S. FDA prescribing information for andexanet alfa includes a black box warning regarding the risk of venous and arterial thromboembolic events.[185]

In summary, we caution against the off-label use of andexanet alfa for reversal of anticoagulant activity of apixaban or rivaroxaban in acute ischaemic stroke patients who are otherwise eligible for IVT.

8.13 - Potential risk factors for bleeding

An increased risk of bleeding after IVT can be suspected in many clinical situations, but the literature search identified no RCT to guide treatment in such situations. Many observational studies have focused on this topic, often comparing outcomes after IVT in patients with and without a bleeding-prone condition.

Although this might identify risk factors for ICH, RCTs would be needed to formally demonstrate or discard a greater harm with IVT in patients with these factors.

Weak recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, and with known platelet count $<100\times10^9$ /L, we suggest no intravenous thrombolysis.

Quality of evidence: Very low

Rationale

PICO 13.1 In patients with acute ischaemic stroke of <4.5 h duration, who have low platelet count, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Patients with a platelet count below $100,000/\text{mm}^3$. A platelet count below $100 \times 10^9/\text{L}$ ($100,000/\text{mm}^3$) was an exclusion criterion in all RCTs of IVT with alteplase except ECASS I and IST-3. We could not find a subgroup analysis of patients with a platelet count below $100 \times 10^9/\text{L}$ in these two trials. In an observational study from ten European centres including 7,533 patients given alteplase, 595 (7.9%) had thrombocytopenia ($<150 \times 10^9/\text{L}$) and 44 (0.6%) a platelet count below $100 \times 10^9/\text{L}$.[157] Thrombocytopenia was not associated with poor functional outcome (mRS score 3–6) at three months (adjusted OR 0.92, 95% CI: 0.73–1.17, P=0.50) or death, but was significantly associated with a higher risk of sICH (adjusted OR 1.68, 95% CI: 1.21–2.36, P=0.002). Compared with other patients, those with a platelet count below $100 \times 10^9/\text{L}$ more often had poor outcome (59.1% vs. 43.1%, P=0.03), but this association did not reach significance in a multivariable analysis (adjusted OR 1.63, 95% CI: 0.82–3.24, P=0.16). Similar point estimates were observed for death (adjusted OR 1.42, 95% CI: 0.66–3.07, P=0.37) and sICH (adjusted OR 1.60, 95% CI: 0.49–5.21, P=0.43).

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and with unknown platelet count before initiation of intravenous thrombolysis and no reason to expect abnormal values, we recommend starting intravenous thrombolysis with alteplase while waiting for lab tests results.

Quality of evidence: Very low

Rationale

Analysis of current evidence.

In our review of the literature, excluding case series, we found that, among 12,701 patients treated with alteplase for acute ischaemic stroke, a total of 66 (0.5%) patients had a platelet count below 100×10^9 /L, of which 4 had sICH (incidence rate 6.1%, 95% CI: 2.4–14.6).[142][157][186][187][188][189] Amongst patients with< 100×10^9 platelets/L in the study by Gensicke et al., median platelet count was 90×10^9 /L (IQR 71–96).[157] Other observational studies have indicated that the proportion of stroke patients with a platelet count < 100×10^9 /L is below 0.5%.[190][191] It is therefore likely that the benefit of earlier IVT would outweigh the harm of bleeding from inadvertently treating patients with a low platelet count.

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration and with major surgery on a non-compressible site where bleeding is likely to lead to significant haemorrhage (e.g., abdomen, chest, skull, well-vascularized tissues, or large artery) during the preceding 14 days, we recommend no intravenous thrombolysis.

Quality of evidence: Very low

Rationale

PICO 13.2 In patients with acute ischaemic stroke of <4.5 h duration, who have a history of recent trauma, surgery, or biopsy, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Significant trauma within the last three months is a contraindication for IVT with alteplase according to the European license.[192] The outcome of IVT in patients with this contraindication has been reported in small case series.[193][194] A relatively high number of patients had serious intracranial or systemic haemorrhage, although there is a possibility of publication bias.

Major surgery, which can be defined as surgery of the abdomen, chest, skull or well-vascularized tissues or of any large artery,[195] has also been an exclusion criteria in all RCTs if performed within 14 days before stroke onset and is therefore also listed as a contraindication on the drug label. Among 4,848 patients treated with alteplase in the Telemedical Project for Integrative Stroke Care (TEMPiS) registry, 49 and 85 patients had undergone surgery within the 10 and 11–90 days preceding stroke onset, respectively.[195] In 86 (64%) patients, surgery was classified as major and in 48 (36%) as minor. A total of 9 (7%) patients developed surgical site haemorrhage after IVT, more often after recent than after non-recent surgery. sICH occurred in 9.7% of patients. No information on three-month functional outcome was provided. Other small observational studies of patients treated with alteplase in spite of recent surgery also suggest that surgical site haemorrhage is the main hazard, without evidence of poor neurological outcome.[194][196]

For patients with acute ischaemic stroke of <4.5 h duration, and a history of intracranial haemorrhage, there is insufficient evidence to make an evidence-based recommendation. Please see the Expert consensus statement below.

Quality of evidence: Very low

Rationale

Please click on 'Rationale' under the 'Expert Consensus Statement' section below.

Consensus recommendation

Expert consensus statement

For patients with acute ischaemic stroke of <4.5 h duration and with a history of intracranial haemorrhage, 8 of 9 members suggest intravenous thrombolysis with alteplase in selected cases. For example, intravenous thrombolysis may be considered if a long time has elapsed since the haemorrhage, or if there was a non-recurrent or treated underlying cause for the haemorrhage (e.g. trauma, subarachnoid haemorrhage with subsequent endovascular or surgical aneurysm removal, or use of specific antithrombotic medication).

Rationale

PICO 13.3 In patients with acute ischaemic stroke of <4.5 h duration, who have a history of intracranial haemorrhage, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Patients with history of ICH were excluded from RCTs of IVT with alteplase, and our literature search identified very few observational studies on this topic. In one observational study of 1,212 patients treated with alteplase, only 7 (0.6%) had a history of ICH (hematoma volume: 1–21 cm,3 elapsed time between previous ICH and ischemic stroke: 1.5–12 years), none of whom developed sICH or died after IVT.197 There are also case reports.[189][196][198] A key question is the time elapsed since the intracranial haemorrhage, but unfortunately this information is not provided in most reports.

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration, for whom cerebral microbleed burden is unknown or known to be low (e.g. <10), we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

Rationale

PICO 13.4 In patients with acute ischaemic stroke of <4.5 h duration, who have cerebral microbleeds, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Most patients enrolled in the RCTs of IVT did not undergo MRI before randomisation and therefore their cerebral microbleed (CMB) burden is unknown. In a meta-analysis of 9 observational studies, CMB was observed on pretreatment MRI in 581 (23.4%) patients, and was associated with an increased risk of sICH (RR 2.36, 95% CI: 1.21–4.61, P=0.01; I2=46%), but the incidence rate of sICH remained relatively low (6.5%, 95% CI: 4.8–8.9 in patients with \geq 1 CMB, and 4.4%, 95% CI: 3.5–5.4% in patients without CMB).[199] However, in the very small subgroup of 15 patients (0.8%) with more than 10 CMBs, the incidence rate of sICH was 46.9% (95% CI: 22.8–72.5). In an individual participant data meta-analysis of 1973 patients, presence of \geq 1 and \geq 10 CMBs were observed in 526 (26.7%) and 35 (1.8%) patients, respectively.[200] The association between CMB presence and sICH did not reach statistical

significance (adjusted OR 1.42, 95% CI: 0.86–2.35, P=0,17), but a count of more than 10 CMBs was associated with sICH (adjusted OR 3.65, 95% CI: 1.17–11.42), remote parenchymal haemorrhage (adjusted OR 9.09, 95% CI: 3.25–25.40) and poor functional outcome (adjusted OR 3.99, 95% CI: 1.55–10.22). Increasing CMB burden, defined as a continuous variable, was also independently associated with both sICH and poor functional outcome (mRS score >2) at three months.

Additional information

Susceptibility-weighted imaging (SWI) is more sensitive than T2* for detecting cerebral microbleeds.[201] Therefore, it is not certain how generalisable recommendations based on T2* detected microbleeds are to SWI detected microbleeds, notably regarding the threshold that should be used to define high microbleed burden. However, a systematic review and individual participant data meta-analysis did not find that the type of MRI sequence (SWI vs. T2*) was associated with the risk of sICH following IVT (P=0.74 for the whole sample; P=0.34 in the subgroup of patients with at least one microbleed).[199]

A recent study devised a multistep algorithm to model three-month mRS scores in patients with ≤ 10 versus >10 CMBs who do or do not receive IVT.[202] Parameters were extracted from recently published meta-analyses and included pairwise relationships between CMBs. IVT in patients with >10 CMBs significantly increased the odds of mortality, while the beneficial treatment effect of IVT on clinical outcome was attenuated in patients with >10 CMBs as compared with patients with ≤ 10 CMBs. However, because the general pretest probability of >10 CMBs is low (0.6%–2.7%), the authors hypothesized that pretreatment MRI to quantify CMB burden would be justified only if it delayed IVT by<10 min.

Weak recommendation against

For patients with acute ischaemic stroke of <4.5 h duration, for whom cerebral microbleed burden has been previously reported to be high (e.g. >10), we suggest no intravenous thrombolysis.

Quality of evidence: Low ++

Rationale

PICO 13.4 In patients with acute ischaemic stroke of <4.5 h duration, who have cerebral microbleeds, does IVT with alteplase lead to

better functional outcome than no IVT?

Analysis of current evidence.

Most patients enrolled in the RCTs of IVT did not undergo MRI before randomisation and therefore their cerebral microbleed (CMB) burden is unknown. In a meta-analysis of 9 observational studies, CMB was observed on pretreatment MRI in 581 (23.4%) patients, and was associated with an increased risk of sICH (RR 2.36, 95% CI: 1.21–4.61, P=0.01; I2=46%), but the incidence rate of sICH remained relatively low (6.5%, 95% CI: 4.8–8.9 in patients with \geq 1 CMB, and 4.4%, 95% CI: 3.5–5.4% in patients without CMB).[199] However, in the very small subgroup of 15 patients (0.8%) with more than 10 CMBs, the incidence rate of sICH was 46.9% (95% CI: 22.8–72.5). In an individual participant data meta-analysis of 1973 patients, presence of \geq 1 and \geq 10 CMBs were observed in 526 (26.7%) and 35 (1.8%) patients, respectively.[200] The association between CMB presence and sICH did not reach statistical

significance (adjusted OR 1.42, 95% CI: 0.86-2.35, P=0,17), but a count of more than 10 CMBs was associated with sICH (adjusted OR 3.65, 95% CI: 1.17-11.42), remote parenchymal haemorrhage (adjusted OR 9.09, 95% CI: 3.25-25.40) and poor functional outcome (adjusted OR 3.99, 95% CI: 1.55-10.22). Increasing CMB burden, defined as a continuous variable, was also independently associated with both sICH and poor functional outcome (mRS score >2) at three months.

Additional information

Susceptibility-weighted imaging (SWI) is more sensitive than T2* for detecting cerebral microbleeds.[201] Therefore, it is not certain how generalisable recommendations based on T2* detected microbleeds are to SWI detected microbleeds, notably regarding the threshold that should be used to define high microbleed burden. However, a systematic review and individual participant data meta-analysis did not find that the type of MRI sequence (SWI vs. T2*) was associated with the risk of sICH following IVT (P=0.74 for the whole sample; P=0.34 in the subgroup of patients with at least one microbleed).[199]

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Consensus recommendation

Expert consensus statement

For patients with acute ischaemic stroke within 4.5 h of stroke onset, 9 of 9 members suggest against systematic screening with MRI to assess cerebral microbleed burden before making a treatment decision regarding intravenous thrombolysis.

Strong recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and small to moderate burden of white matter lesions, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Moderate ⊕⊕⊕

Rationale

PICO 13.5 In patients with acute ischaemic stroke of <4.5 h duration, who have cerebral white matter lesions, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

In IST-3 there was no evidence for heterogeneity of treatment effect regarding good functional outcome between patients with and without white matter lesions (P for interaction =0.24).[100] However, in an analysis of patients enrolled in 4 RCTs (IST-3, NINDS, ECASS-1, ECASS-2; n=2234), IVT with alteplase was associated

with a higher incidence rate of sICH in patients with white matter lesions (7.9%, 95% CI: 6.4–9.6) than in patients without (1.3%, 95% CI: 0.8–2.2; Table 11). Still, IVT was associated with a lower risk of poor functional outcome in patients with white matter lesions, compared with no IVT (OR 0.75, 95% CI: 0.60–0.95, P=0.015; I2=23%).[203]

In a study-level meta-analysis of observational data from 5910 patients treated with alteplase, presence of white matter lesions on CT was associated with sICH (OR 1.55, 95% CI: 1.17–2.06, P=0.002; 7 studies; I2=21%).[203] Severe white matter lesion burden, mostly defined as a score >2 on the Van Swieten scale, was strongly associated with sICH after treatment (OR 2.53, 95% CI: 1.92–3.34, p<0.001; I2=0%). In the 818 patients with severe white matter lesions, the incidence rate of sICH was 9.9% (95% CI: 8.0–12.1). Presence of white matter lesions was associated with poor functional outcome after IVT (OR 2.02, 95% CI: 1.54–2.65, p<0.001; I2=74%), but this association may have been caused by confounding, as larger white matter lesions volumes on MRI are independently associated with worse three-month functional outcome.[204]

Additional information

In an observational study of 2,485 patients treated with alteplase, severe white matter lesions on CT, defined as a Blennow rating scale score of 5 or 6, was independently associated with remote parenchymal hemorrhage (adjusted OR 6.79, 95% CI: 2.57–17.94), but not with parenchymal hemorrhage strictly within the ischemic area (adjusted OR 1.45, 95% CI: 0.83–2.53).[205] Another study, based on MRI volumetric evaluations of white matter lesions, confirmed that larger whole brain corrected white matter lesion volume was associated with remote ICH, irrespective of the deep or periventricular location of white matter lesions.[206]

Clinical Question/ PICO

Population: Patients with acute ischaemic stroke of < 4.5 h duration, who have cerebral white matter lesions

Intervention: IVT with alteplase

Comparator: No IVT

Outcome Timeframe	Study results and measurements	Absolute e No IVT	ffect estimates IVT with alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
Favourable functional outcome 3-6 months	Odds Ratio 1.33 (CI 95% 1.05 - 1.67) Based on data from 2,234 patients in 4 studies. (Randomized controlled)		348 per 1000 2 more per 1000 more - 115 more)	Moderate Due to serious indirectness ¹	IVT with alteplase probably increases favourable functional outcome compared to no IVT.
sICH	Odds Ratio 5.5 (CI 95% 2.49 - 12.13) Based on data from 2,234 patients in 4 studies. (Randomized controlled)		68 per 1000 6 more per 1000 more - 127 more)	High Due to serious indirectness, Upgraded due to very strong association ²	IVT with alteplase increases risk of sICH compared to no IVT.

- 1. Inconsistency: No serious. Indirectness: Serious. This result corresponds to presence or absence of leukoaraiosis. It therefore does not directly address the situation of patients with extensive leukoaraiosis.. Imprecision: No serious. Of note, there was no evidence that presence of leukoaraiosis modifies the effect of IVT on functional outcome in IST-3 (P for interaction \(\frac{1}{2} \) 0.24).. Publication bias: No serious.
- 2. **Inconsistency:** No serious. Indirectness: Serious. This result corresponds to presence or absence of leukoaraiosis. It therefore does not directly address the situation of patients with extensive leukoaraiosis.. **Imprecision:** No serious. There was no evidence in IST-3 that presence of leukoaraiosis significantly modifies the effect of IVT on siCH (P for interaction 40.14). **Publication bias:** No serious. **Upgrade:** Very large magnitude of effect. very strong association.

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration, and high burden of white matter lesions, we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

Rationale

PICO 13.5 In patients with acute ischaemic stroke of <4.5 h duration, who have cerebral white matter lesions, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

In IST-3 there was no evidence for heterogeneity of treatment effect regarding good functional outcome between patients with and without white matter lesions (P for interaction =0.24).[100] However, in an analysis of patients enrolled in 4 RCTs (IST-3, NINDS, ECASS-1, ECASS-2; n=2234), IVT with alteplase was associated

with a higher incidence rate of sICH in patients with white matter lesions (7.9%, 95% CI: 6.4–9.6) than in patients without (1.3%, 95% CI: 0.8–2.2; Table 11). Still, IVT was associated with a lower risk of poor functional outcome in patients with white matter lesions, compared with no IVT (OR 0.75, 95% CI: 0.60–0.95, P=0.015; I2=23%).[203]

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on CT was associated with sICH (OR 1.55, 95% CI: 1.17–2.06, P=0.002; 7 studies; I2=21%).[203] Severe white matter lesion burden, mostly defined as a score >2 on the Van Swieten scale, was strongly associated with sICH after treatment (OR 2.53, 95% CI: 1.92–3.34, p<0.001; I2=0%). In the 818 patients with severe white matter lesions, the incidence rate of sICH was 9.9% (95% CI: 8.0–12.1). Presence of white matter lesions was associated with poor functional outcome after IVT (OR 2.02, 95% CI: 1.54–2.65, p<0.001; I2=74%), but this association may have been caused by confounding, as larger white matter lesions volumes on MRI are independently associated with worse three-month functional outcome.[204]

Additional information

In an observational study of 2,485 patients treated with alteplase, severe white matter lesions on CT, defined as a Blennow rating scale score of 5 or 6, was independently associated with remote parenchymal hemorrhage (adjusted OR 6.79, 95% CI: 2.57–17.94), but not with parenchymal hemorrhage strictly within the ischemic area (adjusted OR 1.45, 95% CI: 0.83–2.53).[205] Another study, based on MRI volumetric evaluations of white matter lesions, confirmed that larger whole brain corrected white matter lesion volume was associated with remote ICH, irrespective of the deep or periventricular location of white matter lesions.[206]

Clinical Question/ PICO

Population: Patients with acute ischaemic stroke of < 4.5 h duration, who have cerebral white matter lesions

Intervention: IVT with alteplase

Comparator: No IVT

Outcome Timeframe	Study results and measurements	Absolute effect estim No IVT IVT with	ates (Quality of evidence)	Plain text summary
Favourable functional outcome 3-6 months	Odds Ratio 1.33 (CI 95% 1.05 - 1.67) Based on data from 2,234 patients in 4 studies. (Randomized controlled)			IVT with alteplase probably increases favourable functional outcome compared to no IVT.
sICH	Odds Ratio 5.5 (CI 95% 2.49 - 12.13) Based on data from 2,234 patients in 4 studies. (Randomized controlled)		70.7 50.51.8	IVT with alteplase increases risk of sICH compared to no IVT.

- 1. **Inconsistency:** No serious. Indirectness: Serious. This result corresponds to presence or absence of leukoaraiosis. It therefore does not directly address the situation of patients with extensive leukoaraiosis.. **Imprecision:** No serious. Of note, there was no evidence that presence of leukoaraiosis modifies the effect of IVT on functional outcome in IST-3 (P for interaction 40.24).. **Publication bias:** No serious.
- 2. **Inconsistency:** No serious. Indirectness: Serious. This result corresponds to presence or absence of leukoaraiosis. It therefore does not directly address the situation of patients with extensive leukoaraiosis.. **Imprecision:** No serious. There was no evidence in IST-3 that presence of leukoaraiosis significantly modifies the effect of IVT on siCH (P for interaction \(^1/4\). **Publication bias:** No serious. **Upgrade:** Very large magnitude of effect. very strong association.

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration, who have an unruptured cerebral artery aneurysm, we suggest IVT with alteplase.

Quality of evidence: Very low

Rationale

PICO 13.6 In patients with acute ischaemic stroke of <4.5 h duration, who have an unruptured cerebral aneurysm, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

The discovery of unruptured aneurysms in the acute phase of stroke is becoming more frequent with the increasing use of cerebral artery imaging. Data on IVT in patients with unruptured aneurysms is scarce. In a systematic review and meta-analysis of observational data, the incidence of sICH among 120 patients treated with alteplase for acute ischaemic stroke and having unruptured intracranial aneurysms was 6.7% (95% CI: 3.1–13.7%).[207] The mean maximum diameter of the aneurysms was 4.3±2.7 mm. The risk of sICH did not significantly differ between patients with and without unruptured aneurysms (RR 1.60; 95% CI: 0.54–4.77, P=0.40; I2=22%). No case of cerebral artery aneurysm rupture was reported in this study.

8.14 - Other co-existing conditions

For patients with acute ischaemic stroke of <4.5 h duration, and with a history of ischaemic stroke during the last three months, there is insufficient evidence to make an evidence-based recommendation recommendation. Please see the Expert consensus statement below.

Quality of evidence: Very low

Rationale

Please click on 'Rationale' under the 'Expert Consensus Statement' section below.

Consensus recommendation

Expert consensus statement

For patients with acute ischaemic stroke of <4.5 h duration, and a history of ischemic stroke within the last three months, nine of nine members voted for intravenous thrombolysis with alteplase in selected cases, for example in case of a small infarct, stroke occurring more than one month earlier, or good clinical recovery.

Rationale

PICO 14.1 In patients with acute ischaemic stroke of <4.5 h duration, who have a history of ischaemic stroke during the last three months, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Patients with coexisting conditions thought to increase the risk of sICH or worse outcome were excluded from the RCTs of IVT with alteplase. One such example is 'history of ischaemic stroke during the last three months', which was also used as an

exclusion criterion in trials of alteplase for acute myocardial infarction.[122] In an observational study of alteplase for acute ischaemic stroke, 14(1.5%) of 946 patients had had a prior stroke within three months.[146] The risk of poor outcome (mRS 3–6 at three months) was nonsignificantly increased in these patients (adjusted OR 4.07, 95% CI: 0.97–17.1). In an analysis of the SITSEAST registry, 249(2%) of 13,007 patients had a stroke in the preceding three months, but it was not independently associated with poor functional outcome defined as an mRS score 3–6 at three months (adjusted OR 0.74, 95% CI: 0.35–1.56) or sICH (adjusted OR 0.74, 95% CI: 0.35–1.56).[208] Other observational studies have shown similar results.[196][209][210][211] In addition, a large study using administrative data from 36,599 patients treated with alteplase found that ischaemic stroke during the last three months was not associated with an increased risk of ICH (adjusted OR 0.9, 95% CI: 0.6–1.4, P=0.62), but was related to an increased risk of death (OR 1.5, 95% CI: 1.2–1.9, P=0.001) and unfavourable discharge disposition (OR 1.3, 95% CI:

1.0-1.7, P=0.04).[212] Finally, a meta-analysis of observational studies including 52,631 patients treated with alteplase found no evidence of increased risk of sICH, death or poor functional outcome or mortality in the 1.7% of patients who had a history of ischaemic stroke during the last three months.[213]

Additional information

These observational studies have a number of limitations. Relatively few patients had had an ischaemic stroke within the previous three months, and many studies did not provide data on the baseline characteristics of these patients. Importantly, most studies did not report the time since the previous ischaemic stroke, precluding definitive conclusions about the minimal time interval that should be respected before using IVT in such patients.

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration who have seizures at time of stroke onset, and for whom there is no suspicion of a stroke mimic or significant head trauma, we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Very low

Rationale

PICO 14.2 In patients with acute ischaemic stroke of <4.5 h duration, who had a seizure at time of stroke onset, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

A seizure can be the initial manifestation of a stroke, but patients with seizures at the time of stroke have been excluded from the RCTs of IVT, for several reasons. First, post-ictal state can mimic a stroke. Second, seizures can also be caused by conditions other than stroke, like structural brain lesions or metabolic/infectious states. Third, a seizure can lead to – sometimes unobserved – head trauma that may increase the risk of secondary ICH.

Data from several observational studies suggests that the risk of sICH is low in patients with stroke mimics[214][215] and also in patients with suspected acute ischaemic stroke with seizure at stroke onset.[216] In an observational study of 5,581 patients treated with alteplase, 100 patients had stroke mimics (1.8%). The rate of sICH in patients with stroke mimics was 1.0% (95% CI: 0.0–5.0) compared with 7.9% (95% CI: 7.2–8.7) in patients with ischaemic strokes.[214] Analysis of data from stroke registries have also provided reassurance that inadvertent administration of alteplase to patients with seizures at onset of stroke-like symptoms does not increase the risk of sICH.[214] However, the possibility of a head trauma as a consequence of the seizure must always be considered.

Additional information

Advanced imaging methods like MRI with DWI and apparent diffusion coefficient (ADC) sequences and perfusion CT although not used in RCTs may be useful to distinguish between postictal deficits and stroke. [217][218] Seizures may be associated with transient peri-ictal MRI abnormalities: a) diffusion abnormalities with mixed appearance with simultaneous acute cytotoxic cortical oedema and vasogenic subcortical oedema without a vascular territory lesion distribution; b) gyral enhancement

occurring earlier than expected for acute ischemic stroke, c) perfusion studies with normal or increased cerebral blood volume (hyperperfusion) at the epileptogenic area during the ictal phase and hypoperfusion in the postictal phase.

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration and with aortic arch dissection we recommend no intravenous thrombolysis.

Quality of evidence: Very low

Rationale

PICO 14.3 In patients with acute ischaemic stroke of <4.5 h duration, who have dissection in the aortic arch, in a carotid artery or in an intracerebral artery, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Most cases of aortic arch dissection receiving IVT with alteplase are patients with acute myocardial infarction. Some of these patients have suffered extension of dissection into the pericardium, leading to cardiac tamponade and death.[219] There are only anecdotal case reports in the literature of patients with acute ischaemic stroke who had an aortic arch dissection and were treated with alteplase. Reported complications include cardiac tamponade and intrapleural haemorrhage.[220][221] IVT in these patients could also reduce the possibility of survival by leading to the postponement of an emergency operation to treat thoracic aortic dissection.[222]

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration and with isolated cervical artery dissections, we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Low ++

Rationale

PICO 14.3 In patients with acute ischaemic stroke of <4.5 h duration, who have dissection in the aortic arch, in a carotid artery or in an intracerebral artery, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Extracranial artery dissection was a not specific exclusion criterion in RCTs of IVT versus placebo, but because dissection is a rare event the number of randomised patients is likely to be very low and no specific subgroup analysis has been published. Few observational studies provide a direct comparison of IVT versus no IVT in patients with artery dissection. The Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) group published an observational

study of 616 patients with extracranial artery dissection, of which 68 (11.0%) received alteplase (81% treated with IVT and 19% with intra-arterial alteplase).[223] After adjustment for stroke severity and large vessel occlusion status, the likelihood of good outcome (mRS 0–2) did not differ between patients treated with alteplase and controls (adjusted OR 0.95, 95% CI: 0.45–2.00). ICH occurred in 4 (5.9%) of the patients who received alteplase (all of which were asymptomatic) and 3 (0.6%) of patients who did not receive alteplase (two of which were asymptomatic). In a small single-centre study of 46 patients with ischaemic stroke due to artery dissection, of which 19 (41%) were treated with IVT, the proportion of good outcome (mRS 0–2) did not significantly differ between patients treated with or without IVT (95% vs. 82%; adjusted OR 5.49; 95% CI: 0.77–39.11).[224] In an unpublished subgroup analysis (n=49) of patients with dissection and internal carotid occlusion from the Systemic

thrombolysis in patients with acute ischemic stroke and Internal Carotid ARtery Occlusion (ICARO) observational study,[225] IVT (n=26) was not significantly associated with excellent (mRS score 0–1) or good (mRS score 0–2) outcome compared with no IVT (unadjusted ORs 2.11, 95% CI: 0.54–8.25 and 1.96, 95% CI: 0.60–6.35, respectively).

Other observational studies provide a comparison of IVT-treated patients with and without dissection. An individual participant data meta-analysis of observational studies including 180 patients with cervical carotid artery dissection indicated that case fatality at three months and risk of sICH was similar in patients with dissection and matched controls (fatality rate 7.3%, 95% CI: 3.7–13.9% vs. 8.8%, 95% CI: 5.1–14.5%, and sICH rate 3.3% 95% CI: 1.2–8.5% vs. rate 5.9% 95% CI: 3.0–10.9%).[226] Similar findings were reported in a meta-analysis of 234 patients with co-existent extra- or intracranial dissections who received alteplase.[227] The respective rates of sICH and death were 2% (0–5%) and 4% (0–8%), underscoring the safety of alteplase in dissection-related acute ischaemic stroke.

The quality of evidence for IVT in patients with isolated cervical artery dissection was rated as low because although extracranial dissection was not a formal exclusion criterion in pivotal RCTs, direct comparison of IVT vs. no IVT in this population relies only on observational studies with important risk of selection bias and confounding by indication. We decided not to perform a meta-analysis of these studies due to notable differences in study design.

For patients with acute ischaemic stroke of < 4.5 h duration and with intracerebral artery dissections, there is insufficient evidence to make a recommendation. Please see the Expert consensus statement below.

Quality of evidence: Very low

Rationale

Please click on 'Rationale' under the 'Expert Consensus Statement' section below.

Consensus recommendation

For patients with acute ischaemic stroke of <4.5 h duration and with an intracerebral artery dissection, 6 of 9 group members suggest against intravenous thrombolysis with alteplase.

Rationale

Additional information

The presence of intracranial arterial dissection may result in subadventitial extension of the hematoma and increase the risk of subarachnoid haemorrhage (especially when located in the posterior circulation) or intracranial bleeding in acute ischaemic stroke patients receiving antithrombotic and thrombolytic treatments.[228]

Weak recommendation against

For patients with acute ischaemic stroke of <4.5 h duration and with history of subacute (>6 h) ST-elevation myocardial infarction during the last seven days, we suggest no IVT.

Quality of evidence: Very low

Rationale

PICO 14.4 In patients with acute ischaemic stroke of <4.5 h duration, who have had myocardial infarction during the last three months, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Myocardial infarction during the last three months was not an exclusion criterion in the completed RCTs, so the results from these trials apply to these patients.

However, there are case reports describing myocardial rupture, cardiac tamponade or embolisation of ventricular thrombus after IVT for acute ischaemic stroke in patients who have had a recent acute myocardial infarction.[229][230][231] Conversely, other case reports describe successful administration of IVT with alteplase in patients with acute ischaemic stroke and recent myocardial infarction. In a systematic review of case series that included 102 patients, four (8.5%) of the 47 IVT-treated patients died from confirmed or presumed cardiac rupture/tamponade, all with subacute (>6 h) ST-elevation Myocardial Infarction (STEMI) in the week preceding stroke.[232] This complication occurred in 1 (1.8%) patients in the non-treated group (P=0.18). No non-STEMI patients receiving IVT with alteplase had cardiac complications.

Non-STEMI patients have a lower risk of complications than transmural STEMI patients, and among STelevation infarctions, infarctions in the anterior wall have the highest cardiac complication rates.[233] Cardiac complications tend to peak 2–14 days after myocardial infarction.[234]

Additional information

IVT with alteplase at a dose of 1.1 mg/kg is indicated in patients with acute (< 6h) myocardial infarction. Consequently, in the uncommon case scenario of an acute ischaemic stroke complicating an acute myocardial infarction alteplase may be administered if there are no other contraindications to IVT. The dose and the time window should conform to the recommendations of IVT for acute ischaemic stroke to minimize the risk of sICH.

Mechanical thrombectomy may be a therapeutic alternative to bridging therapy in patients with large vessel occlusion and recent myocardial infarction.

For patients with acute ischaemic stroke of <4.5 h duration and with history of ST-elevation myocardial infarction of more than a week to three months, there is insufficient evidence to make a recommendation. Please see the Expert consensus statement below.

Quality of evidence: Very low

Rationale

Please click on 'Rationale' under the 'Expert Consensus Statement' section below.

Weak recommendation

For patients with acute ischaemic stroke of <4.5 h duration and with a history of non-ST-elevation myocardial infarction during the last three months, we suggest intravenous thrombolysis with alteplase.

Quality of evidence: Very low

Rationale

PICO 14.4 In patients with acute ischaemic stroke of <4.5 h duration, who have had myocardial infarction during the last three months, does IVT with alteplase lead to better functional outcome than no IVT?

Analysis of current evidence.

Myocardial infarction during the last three months was not an exclusion criterion in the completed RCTs, so the results from these trials apply to these patients.

However, there are case reports describing myocardial rupture, cardiac tamponade or embolisation of ventricular thrombus after IVT for acute ischaemic stroke in patients who have had a recent acute myocardial infarction.[229][230][231] Conversely, other case reports describe successful administration of IVT with alteplase in patients with acute ischaemic stroke and recent myocardial infarction. In a systematic review of case series that included 102 patients, four (8.5%) of the 47 IVT-treated patients died from confirmed or presumed cardiac rupture/tamponade, all with subacute (>6 h) ST-elevation Myocardial Infarction (STEMI) in the week preceding stroke.[232] This complication occurred in 1 (1.8%) patients in the non-treated group (P=0.18). No non-STEMI patients receiving IVT with alteplase had cardiac complications.

Non-STEMI patients have a lower risk of complications than transmural STEMI patients, and among STelevation infarctions, infarctions in the anterior wall have the highest cardiac complication rates.[233] Cardiac complications tend to peak 2–14 days after myocardial infarction.[234]

Additional information

IVT with alteplase at a dose of 1.1 mg/kg is indicated in patients with acute (< 6h) myocardial infarction. Consequently, in the uncommon case scenario of an acute ischaemic stroke complicating an acute myocardial infarction alteplase may be administered if there are no other contraindications to IVT. The dose and the time window should conform to the recommendations of IVT for acute ischaemic stroke to minimize the risk of sICH.

Mechanical thrombectomy may be a therapeutic alternative to bridging therapy in patients with large vessel occlusion and recent myocardial infarction.

Consensus recommendation

Expert consensus statement

For patients with acute ischaemic stroke of <4.5 h duration and with history of ST-elevation myocardial infarction of more than a week to three months, nine of nine group members suggest IVT with alteplase in specific situations. Variables to take into account are the size of the myocardial infarction, whether recanalisation therapy was given for the myocardial infarction, and echocardiographic findings.

Strong recommendation against

For patients with acute ischaemic stroke of <4.5 h duration and with a clear or suspected diagnosis of infective endocarditis, we suggest no intravenous thrombolysis.

Quality of evidence: Low ++

Rationale

PICO 14.5 In patients with acute ischaemic stroke of <4.5 h duration, who have infective endocarditis, does IVT with alteplase lead to

better functional outcome than no IVT?

Analysis of current evidence.

Stroke is the most common neurological complication of infective endocarditis, affecting up to 35% of all patients.[235] Histopathological studies also suggest that cerebral infarcts caused by septic emboli are particularly prone to haemorrhagic transformation as a result of septic arteritis with erosion of the arterial wall in the

recipient vessel, with or without the formation of mycotic aneurysms.[236] Consequently, there are theoretical reasons to expect that IVT for acute ischaemic stroke due to infective endocarditis will be associated with a higher risk of sICH.[222] In a large study based on administrative data, the outcome of patients treated with IVT for acute ischaemic stroke with (n=222) and without (n=134,048) infective endocarditis was compared. The rate of post-thrombolytic ICH was significantly higher in patients with infective endocarditis than in those without (20% versus 6.5%, P=0.006), and the proportion of patients with discharge disposition of home/self-care was significantly lower in the infective endocarditis group (10% versus 37%, P=0.01).[237] Some studies have also shown that alteplase in patients with co-existing infective endocarditis may be complicated with multifocal ICH.[238][239]

9 - Discussion

This guideline document was developed following the GRADE methodology and aims to assist physicians in decision-making regarding IVT for acute ischaemic stroke. It includes up-to-date scientific evidence that supersedes the previously published ESO guidelines and Karolinska Stroke Update recommendations.[1][240] All recommendations and Expert consensus statements are summarized in Table 12.

Whenever possible, we based our recommendations on RCTs or individual participant data meta-analyses of RCTs rather than observational studies, which are more prone to selection bias and confounding. We found that there is high quality evidence for recommendations on time to treatment, patients with different ages and stroke severity, based on individual participant data analyses of all trials of IVT with alteplase to date.

We decided to provide separate recommendations for patients with unknown symptom onset and patients with known stroke onset of more than 4.5 hrs, because we believe that they correspond to two distinct clinical scenarios. Indeed, many patients with wake-up stroke may have a 'true' stroke onset of <4.5 hrs.[31],[32] Therefore, from a pathophysiological standpoint, this situation notably differs from strokes of more than 4.5hrs' duration. Furthermore, in our experience the information on whether the symptom onset is known or unknown is generally available when the patient arrives in the hospital. Based on the result of an individual participant data meta-analysis of RCTs,[46] we recommend IVT in patients with unknown stroke onset selected with advanced imaging (DWI-FLAIR mismatch or core/perfusion mismatch). An extension of the time window beyond 4.5 h of known onset time is also possible if perfusion-diffusion MRI or CT perfusion shows potentially salvageable brain tissue. However, urgent advanced brain imaging is not always available, which may limit the immediate applicability of these recommendations. Moreover, the recent trials on the extended time window -EXTEND and ECASS-4- excluded patients for whom mechanical thrombectomy was planned, which may further reduce the number of patients qualifying for IVT beyond 4.5 h. Although there are several high-quality trials to guide practice, 29 out of 40 recommendations are based on low or very low quality of evidence. These recommendations came from meta-analyses of small trials, single modest-sized randomised trials, or observational studies. Although tenecteplase has a number of potential advantages, it is remains uncertain whether it is non-inferior to alteplase for all patients with acute ischaemic stroke. Still, we found low quality evidence to suggest tenecteplase over alteplase in patients with large vessel occlusion who are candidates for mechanical thrombectomy.

The strengths of this guideline are its systematic approach to searching the literature and guidance by the GRADE recommendations. However, many questions posed to the guideline module working group were about particular subgroups of patients with different clinical characteristics, or who were taking particular drugs at baseline. In many of these patients there are clinical uncertainties about the balance of benefit and harm of IVT. However, in the absence of studies randomly allocating participants in these subgroups to IVT or control, the precise effects of treatments are unknown. It would be a mistake to interpret a modestly higher risk of post-IVT sICH as a reason not to treat such patients, because the benefit of alteplase has not been similarly quantified. Therefore, for almost all patients the best prediction of effect of IVT is that of the average patient treated at that time point in a randomised trial rather than patient with very similar characteristics from an observational study. However, for practical reasons not all remaining questions regarding IVT can be answered by RCTs. Multicentre registries offer observational evidence that could contribute to our knowledge on IVT, particular when they are representative of all treated patients.

To support physicians in their practical decisionmaking, expert consensus statements are given in a dedicated paragraph. Whenever appropriate, these opinions were systematically collected as polls. About three out of four of these polls (13/17) led to a good agreement of 7–9 of the 9 group members. In the remaining questions, the group members' opinions varied considerably. The recommendations with very low evidence and poor agreement among experts were on the subjects of IVT before thrombectomy in wake-up stroke or ischaemic stroke of 4.5–9 h duration, especially in those patients directly admitted to a thrombectomy-capable centre.

A next priority of research into thrombolysis is how to implement it widely in populations with the greatest need – that is patients in those areas with the highest stroke incidence and lowest use of thrombolysis. This will need methods to make decisions about IVT as rapid and as simple as possible and remove certain barriers related to initial exclusion criteria that are not supported by current randomised or observational evidence. Implementation studies, training, further improvement in safety of IVT, reducing the cost of thrombolytics and resource allocation to stroke in the areas of Europe with the highest stroke incidence are most likely to give the greatest return on investment.

10 - Disclaimers

10.1 - Declaration of conflicting interests

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: All disclosures are listed in Supplemental Table 1

10.2 - Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

10.3 - Ethical approval

No ethical approval was needed for this manuscript, which is an ESO Guideline.

10.4 - Informed consent

Not relevant for this type of manuscript.

10.5 - Guarantor

G Turc

10.6 - Contributorship

EB, WW and G Turc conceived the study. All authors searched the literature. G Turc, GMDM and G Tsivgoulis conducted the statistical analysis. All authors contributed to writing the first draft of the manuscript, under the supervision of EB, WWand G Turc. All authors reviewed and edited the manuscript several times and approved the final version of the manuscript.

10.7 - Acknowledgments

We thank Joshua Cheyne for his help with the systematic review of the literature.

ESO would like to thank Ying Wang for migrating the guideline into MAGICapp.

11 - Supplemental material

Supplemental Table 1: Intellectual and financial disclosures of the module working group members

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Gian Marco De Marchis	Neurologist, Neurology and Stroke Center; Department of Clinical Research, University Hospital of Basel, University of Basel, Basel, Switzerland	Intellectual disclosures: Co-Investigator in an advisory role in the TWIS (NCT03181360). Sponsor of trial is University Hospital of North Norwa will reimburse the sponsor for the costs of tenecteplase in the trial. Co-Stroke trial (NCT04304508) sponsored by BAYER. Financial disclosures: Support from the Swiss National Science Foundar Spezialprogramm Nachwuchsförderung Klinische Forschung, University (Wissenschaftspool) of the University Hospital Basel; Swiss Heart Foun Swisslife Jubiläumsstiftung for Medical Research; Swiss Neurological Science De Quervain research grant; Thermo Fisher GmbH; travel honoraria by honoraria by Bayer and Medtronic. Industry support is devolved to a red Hospital of Basel.
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Georgios Tsivgoulis	Neurologist, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece & Department of Neurology, University of Tennessee Health Science Center, Memphis, Tennessee, USA	Intellectual disclosures: - Consulting Editor for Stroke - Associate Editor for Therapeutics advances in Neurological Disorders Financial disclosures: - Participation in advisory meetings & satellite symposia for Boehringer Biogen, Genesis Pharma, Teva, Merck-Serono, Bayer, Daichii-Sankyo, Al Medtronic, CSL Behring. - Unrestricted research grants from Novartis, Genesis Pharma, Teva, Shi Boehringer-Ingelheim, Allergan
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