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Evidence Based Health Care

# Stroke

# Clinical Practice Guideline on the Use of Thrombolytic Therapy in Acute Stroke

April 2014

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# Executive summary

## Introduction

Stroke is a common disease that is associated with significant morbidity and mortality. A single center study in Kingdom of Saudi Arabia showed a prevalence of stroke to be 29 per 100,000 per year.[1] Reperfusion of ischemic brain tissue may be achieved with the use of thrombolytic therapy. Recombinant tissue plasminogen activator (r-tPA) is used widely to treat patients presenting with acute ischemic stroke; however there is variation in the safety and efficacy of this intervention that depends on multiple factors. Given this, the Ministry of Health of the Kingdom of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making.

## Methodology

This clinical practice guideline is a part of the larger initiative of the Ministry of Health of the Kingdom of Saudi Arabia (KSA) to establish a program of rigorous adaptation and de novo development of guidelines. The ultimate goals are to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the "Antithrombotic and Thrombolytic Therapy for Ischemic Stroke" chapter of the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, 9th edition (see **Appendix 1**). We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[2] We used this information to prepare the evidence to recommendation tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 2**). The guideline panel met in Riyadh on December 3, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

## How to use these guidelines

The guideline working group developed and graded the recommendations and assessed the quality of the supporting evidence according to the GRADE approach.[4] Quality of evidence (confidence in the available estimates of treatment effects) is categorized as: high, moderate, low, or very low based on consideration of risk of bias, directness, consistency and precision of the estimates. High quality evidence indicates that we are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality evidence indicates moderate confidence, and that the true effect is likely close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality evidence indicates that our confidence in the effect estimate is limited, and that the true effect may be substantially different. Finally, very low quality evidence indicates that the estimate of effect of interventions is very uncertain, the true effect is likely to be substantially different from the effect estimate and further research is likely to have important potential for reducing the uncertainty.

The strength of recommendations is expressed as either strong ('guideline panel recommends…') or conditional ('guideline panel suggests…') and has explicit implications (see Table 1). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

**Table 1: Interpretation of strong and conditional (weak) recommendations**

| Implications | Strong recommendation | Conditional (weak) recommendation |
|---|---|---|
| For patients | Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. | The majority of individuals in this situation would want the suggested course of action, but many would not. |
| For clinicians | Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. | Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences. |
| For policy makers | The recommendation can be adapted as policy in most situations | Policy making will require substantial debate and involvement of various stakeholders. |

## Key questions

1. Should intravenous IV r-tPA be used in patients with acute ischemic stroke and symptoms onset less than 3 hours, when compared to no r-tPA?
2. Should IV r-tPA be used in patients with acute ischemic stroke and symptoms onset between 3 and 4.5 hours, when compared to no r-tPA?
3. Should IV r-tPA be used in patients with acute ischemic stroke and symptoms onset between 4.5 and 6 hours, when compared to no r-tPA?
4. Should intra-arterial (IA) r-tPA be used in patients with acute ischemic stroke when compared to no IA r-tPA?
5. Should combination of IV and IA r-tPA in patients with acute ischemic stroke when compared to IV r-tPA alone?
6. Should we use mechanical thrombectomy in patients with acute ischemic stroke when compared to no thrombectomy?

## Recommendations

**Recommendation 1:**
**The Ministry of Health of Saudi Arabia panel recommends using IV r-tPA in patients with acute ischemic stroke presenting within 3 hours of symptoms onset** (Strong recommendation, high quality of evidence).

*Remark:*
Patients with high bleeding risk and resulting concerns about thrombolytic therapy should not receive r-tPA. There should be more attention toward improving the feasibility and overcoming barriers to implementation. This may include enhancing public awareness and education, establishment of stroke units, availability of physicians, radiologists and radiology technicians, and incentives to compensate for workload and working hours. Centers that are equipped to administer IV r-tPA may refer to and implement the internationally available quality measures, for example recording mortality, disability and ICH rates, rate of thrombolytic therapy use and door to needle time.

**Recommendation 2:**
**The Ministry of Health of Saudi Arabia panel suggests using IV r-tPA in patients with acute ischemic stroke presenting between 3 to 4.5 hours of symptoms onset. (Weak recommendation, low quality of evidence).**

*Remark:*
Patients with high bleeding risk and resulting concerns about thrombolytic therapy should not receive r-tPA. The generalizability of this recommendation to patients with diabetes mellitus and old stroke, and patients with large stroke (NIHSS>25) is less certain.

**Recommendation 3:**
**The Ministry of Health of Saudi Arabia panel recommends against using IV r-tPA in patients with acute ischemic stroke presenting after 4.5 hours of symptoms onset. (Strong recommendation, moderate quality of evidence).**

**Recommendation 4:**
**The Ministry of Health of Saudi Arabia panel suggests using IA r-tPA initiated within 6 hours of symptoms onset in patients with acute ischemic stroke due to proximal cerebral artery occlusion or patients who cannot receive IV r-tPA. (Weak recommendation, low quality of evidence).**

*Remark:*
Studies contributing to this recommendation included exclusively patients with middle cerebral artery (MCA) occlusion. Resources required to implement this intervention are large, it requires availability of equipment and trained healthcare providers. This recommendation may not apply to centers that are not equipped to administer IA r-tPA.

**Recommendation 5:**
**The Ministry of Health of Saudi Arabia panel suggests not using combination of IV and IA r-tPA over IV r-tPA. (Weak recommendation, very low quality of evidence)**

**Recommendation 6:**
**The Ministry of Health of Saudi Arabia panel suggests against using mechanical thrombectomy in the management of patients with acute ischemic stroke. (Weak recommendation, low quality of evidence).**

*Remark:*
Some carefully selected patients who value the uncertain benefits of mechanical thrombectomy more than the associated risk may choose this intervention.

# Scope and purpose

The purpose of this document is to provide guidance about thrombolytic treatment of acute stroke. The target audience of these guidelines includes neurologists, critical care specialists, specialists in internal medicine, and hospitalists in the Kingdom of Saudi Arabia. Specialists in emergency medicine, other health care professionals and policy makers may also benefit from these guidelines. This clinical practice guideline is a part of the larger initiative of the Ministry of Health of Saudi Arabia to establish a program of rigorous adaptation and de novo development of guidelines in the Kingdom; the ultimate goal being to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

# Introduction

Stroke is a common disease that is associated with significant morbidity and mortality. A single center study in the KSA showed a prevalence of stroke to be 29 per 100,000 per year[1]; larger and methodologically sound studies are required to accurately describe the prevalence of stroke in the KSA. Although the burden of stroke on health care system in the KSA appears to be large, there are no data to quantify the impact on patients, policy makers and health care providers.

Reperfusion of ischemic brain tissue may be achieved with the use of thrombolytic therapy. Recombinant tissue plasminogen activator (r-tPA) is used widely to treat patients presenting with acute ischemic stroke, however there is variation in the safety and efficacy of this intervention that depends on multiple factors. Given the importance of this topic, the Ministry of Health of the Kingdom of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making.

# Methodology

To facilitate the interpretation of these guidelines; we briefly describe the methodology we used to develop and grade recommendations and quality of the supporting evidence. We present the detailed methodology in a separate publication.[5]

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the "Antithrombotic and Thrombolytic Therapy for Ischemic Stroke" chapter of the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, 9th edition (see **Appendix 1**).[6] We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach (see **Appendix 2**).[2]

We assessed the quality of evidence using the system described by the GRADE working group.[4] Quality of evidence is classified as "high", "moderate", "low", or "very low" based on decisions about methodological characteristics of the available evidence for a specific health care problem. The definition of each category is as follows:

- *High*: We are very confident that the true effect lies close to that of the estimate of the effect.
- *Moderate*: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- *Low*: Our confidence in the effect estimate is limited: The true effect may

be substantially different from the estimate of the effect.
- *Very low*: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

According to the GRADE approach, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision-making.

Based on this information and the input of KSA MoH panel members we prepared the evidence-to-recommendation tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 2**). The guideline panel met in Riyadh on December 3, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

# How to use these guidelines

The Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guidelines provide clinicians and their patients with a basis for rational decisions in the management of ischemic stroke. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No guidelines and recommendations can take into account all of the often-compelling unique features of individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate an accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines.

# Key questions

The following is a list of the clinical questions selected by the KSA guideline panel and addressed in this guideline. For details on the process by which the questions were selected please refer to the separate methodology publication.[5]

1. Should intravenous IV r-tPA be used in patients with acute ischemic stroke and symptoms onset less than 3 hours, when compared to no r-tPA?
2. Should IV r-tPA be used in patients with acute ischemic stroke and symptoms onset between 3 and 4.5 hours, when compared to no r-tPA?
3. Should IV r-tPA be used in patients with acute ischemic stroke and symptoms onset between 4.5 and 6 hours, when compared to no r-tPA?
4. Should intra-arterial (IA) r-tPA be used in patients with acute ischemic stroke when compared to no IA r-tPA?
5. Should combination of IV and IA r-tPA in patients with acute ischemic stroke when compared to IV r-tPA alone?
6. Should we use mechanical thrombectomy in patients with acute ischemic stroke when compared to no thrombectomy?

# Recommendations

**I. Treatment with IV r-tPA within 3 hours of stroke onset:**

**Question 1: Should intravenous IV r-tPA be used in patients with acute ischemic stroke and symptoms onset less than 3 hours, when compared to no r-tPA?**

*Summary of findings:*
A recent systematic review[7] that included data from seven randomized controlled trials (RCTs)[8-14] showed that the use of IV r-tPA improve the functional status without significant effect on mortality [Table2]. We identified one new RCT (*International Stroke Trial III*) that examined the effect of IV r-tPA in patients presenting within 6 hours of symptoms onset. Data on subgroup of patients treated within 3 hours was included in this systematic review[14].

Although ICH is an important outcome it was not considered separately because it is captured by mortality and good functional outcomes. The overall quality of evidence was judged to be "High", although there was a 13% relative risk increase (1.4% absolute increase) in the risk of death, the panel members judged the risk to be small in the face of large benefit, hence the estimates of treatment effect were considered precise enough not to lower for imprecision [Table 2].

*Values and preferences:*
There are no published data on values and preferences. However, extrapolating from literature existing in other countries,[15] this recommendation places higher value for being alive and functional compared to being alive and disabled.

*Cost effectiveness:*
There are no published or unpublished data on the cost effectiveness of IV r-tPA in the context of Saudi Arabia. However, multiple cost-effectiveness (CE) studies from different regions in the world have shown that r-tPA is probably cost effective when used within 3 hours of the onset of stroke symptoms[16]. This recommendation considers that the intervention to be cost effective in the view of the large treatment effect and CE studies from other regions in the world.

**Recommendation 1:**

The Ministry of Health of Saudi Arabia panel recommends using IV r-tPA in patients with acute ischemic stroke presenting within 3 hours of symptoms onset (Strong recommendation, high quality of evidence).

*Remarks:*
Patients with high bleeding risk and resulting concerns about thrombolytic therapy should not receive r-tPA. There should be more attention toward improving the feasibility and overcoming barriers to implementation. This may include enhancing public awareness and education, establishment of stroke units, availability of physicians, radiologists and radiology technicians, and incentives to compensate for workload and working hours.
Centers that are equipped to administer IV r-tPA may refer to and implement the internationally available quality measures, for example recording mortality, disability and ICH rates, rate of thrombolytic therapy use and door to needle time.

**II. Treatment with IV r-tPA within 3 to 4.5 hours of stroke onset:**

**Question 2: Should IV r-tPA be used in patients with acute ischemic stroke and symptoms onset between 3 and 4.5 hours, when compared to no IV r-tPA?**

*Summary of findings:*
A recent systematic reviews[17] that included data from five RCTs[10-12,18,19] showed that the use of IV r-tPA improve the functional status without significant effect on mortality [Table 3]. We identified no new RCTs or systematic reviews; although the IST III randomized patients to receive IV r-tPA within 6 hours of symptoms onset, data on patients receiving the treatment between 3 and 4.5 hours was not available[14]. The quality of evidence for was judged to be "low" for mortality outcome and "high" for good functional outcome [Table 3].

*Subgroups:*
The ECASS III is the largest trial contributing to the analysis; patients with diabetes mellitus, patients older than 80 years, and patients with large stroke (NIHSS > 25) were excluded from this trial[18]. Hence, the generalizability of the results to patients with these characteristics is less certain.

*Values and preferences:*
This recommendation places higher value on being alive and functional compared to being alive and disabled and the risk of adverse consequences.

*Cost effectiveness:*
There are no published or unpublished data on the cost effectiveness of IV r-tPA in the context of Saudi Arabia. However, CE studies from other countries suggested that IV r-tPA may be cost effective if used between 3 and 4.5 hours of the onset of stroke symptoms.[20,21]

*Implementation:*
There are some barriers that will need to be addressed when implementing this intervention including public awareness and education, availability of resources in peripheral regions and smaller cities including availability of radiologists, radiology technicians, and imaging machines (e.g. computed tomography). Referring to available implementation tools from other international institutions may help providing starting basis for implementation in KSA.

*Monitoring and evaluation*:
Referring to available international quality measures is important to ensure standardization of administering the intervention and to detect rate of both benefit and harm. For instance recording the number of centers providing the treatment, mortality, disability and intracranial bleeding rates, door to needle time, and other quality indicators.
*Research priorities:*
A national stroke registry is an important consideration to better understand the demographics and the burden of stroke in KSA. Cost effectiveness studies are also needed to inform future guidelines and stakeholders.

**Recommendation 2:**

The Ministry of Health of Saudi Arabia panel suggests using IV r-tPA in patients with acute ischemic stroke presenting between 3 to 4.5 hours of symptoms onset. (Weak recommendation, low quality of evidence).

*Remarks:*
Patients with absolute contraindication to thrombolytic therapy should not receive r-tPA. The generalizability of this recommendation to patients with diabetes mellitus and old stroke, and patients with large stroke (NIHSS>25) is less certain. There should be more attention toward improving the feasibility and overcoming barriers to implementation. This may include enhancing public awareness and education, establishment of stroke units, availability of physicians, radiologists and radiology technicians, and incentives to compensate for workload and working hours.
Centers that are equipped to administer IV r-tPA may refer to and implement the internationally available quality measures, for example recording mortality, disability and ICH rates, rate of thrombolytic therapy use and door to needle time.

**III. Treatment with IV r-tPA within 4.5 to 6 hours of stroke onset:**

**Question 3: Should IV r-tPA be used in patients with acute ischemic stroke and symptoms onset between 4.5 and 6 hours, when compared to no r-tPA?**

*Summary of findings:*
We did not identify new RCTs or systematic reviews. We could not include results from the IST III due to lack of data on subgroup of patients presenting between 4.5 to 6 hours[14]. Evidence from a systematic review[17] that included data from four RCTs[10-12,19] showed that the use of IV r-tPA was associated with increased risk of death (odds ratio [OR] 1.49; 95% CI 1.0 to 2.21), and no significant increase

in good functional outcomes (OR 1.22; 95% CI 0.96 to 1.54). The overall quality of evidence is "moderate" [Table 4].

**Recommendation 3:**

The Ministry of Health of Saudi Arabia panel recommends against using IV r-tPA in patients with acute ischemic stroke presenting after 4.5 hours of symptoms onset. (Strong recommendation, moderate quality of evidence).

**IV. Treatment with IA r-tPA:**

**Question 4: Should intra-arterial (IA) r-tPA be used in patients with acute ischemic stroke due to proximal cerebral artery occlusion, when compared to no r-tPA?**

*Summary of findings:*
The updated search did not identify new RCTs or systematic reviews. A meta-analysis of three RCTs[22] showed that the use of IA r-tPA is associated with higher chance of good outcomes (relative risk [RR] 1.44; 95%CI 1.06 to 1.95) or 128 more good outcomes per 1000 treated patients [Table 5]. However, there was uncertainty about the risk of death that ranged between 92 fewer deaths to 69 more deaths per 1000 treated patients. The quality of evidence is "low" for mortality outcome and "moderate" for good functional outcome. Furthermore, r-tPA was not used in any RCT, and all three trials used recombinant prourokinase[23-25]. Hence, the quality of evidence was lowered for indirectness. These RCTs exclusively enrolled patients with MCA occlusions. Data on IA thrombolysis for treatment of patients with other vascular occlusions are therefore limited.

**Recommendation 4:**

The Ministry of Health of Saudi Arabia panel suggests using IA r-tPA initiated within 6 hours of symptoms onset in patients with acute ischemic stroke due to proximal cerebral artery occlusion or patients who cannot receive IV r-tPA (Weak recommendation, low quality of evidence).

*Remarks:*
Studies contributing to this recommendation included exclusively patients with MCA occlusion. Resources required to implement this intervention are large, it requires availability of equipment and trained healthcare providers. This recommendation may not apply to centers that are not equipped to administer IA r-tPA. Cost effectiveness data are lacking for the context of KSA.

**V. Treatment with combination of IV and IA r-tPA:**

**Question 5: Should combination of IV and IA r-tPA in patients with acute ischemic stroke when compared to IV r-tPA alone?**

*Summary of findings:*
Pooling the results of two small observational studies, the effect of combination therapy on mortality and functional outcomes remain uncertain [Table 6].[26,27] The effect estimates include significant harm and benefit, reflecting the imprecision of the results. The overall quality of evidence was "very low". Of note symptomatic ICH occurred in 13 of 161 patients (8.0%) treated with combined therapy and in 12 of 182 patients (6.6%) treated with IV tPA alone (RR, 1.23; 95% CI, 0.58-2.57).

**Recommendation 5:**

The Ministry of Health of Saudi Arabia panel suggests not using combination of IV and IA r-tPA over IV r-tPA. (Weak recommendation, very low quality of evidence)

**VI. Treatment with mechanical thrombectomy:**

**Question 6: Should we use mechanical thrombectomy in patients with acute ischemic stroke when compared to no thrombectomy?**

*Summary of findings:*
Mechanical thrombectomy involves retrieval of the thrombus from occluded large vessels; it is a complex procedure that requires special

training and skills. A recent RCT comparing the endovascular therapy (mechanical thrombectomy, IA thrombolysis, or a combination of both) with IV r-tPA did not show a statistically significant benefit of endovascular therapy over IV r-tPA for mortality and disability outcomes[28].

Another RCT did not show a statistically significant benefit of combination therapy (IV r-tPA with endovascular therapy) over IV r-tPA alone[29]. A third RCT enrolling patients with acute ischemic stroke within 8 hours of symptoms onset; randomized patients to receive either mechanical thrombectomy or no treatment failed to demonstrate superiority of thrombectomy for mortality and disability outcomes[30]. In this study patients were stratified by presence of favorable penumbral patterns on imaging studies. Prior to randomization, 43% and 30% in the thrombectomy and control groups received IV r-tPA, respectively. Only patients who had persistent vascular occlusion after receiving IV r-tPA were eligible. Moreover, the use of rescue IA r-tPA was allowed; only 8 patients (12.5%) in the thrombectomy group received IA r-tPA. The embolectomy device used in this study (Merci Retriever) is a first-generation device. Recent small RCTs comparing it with new generation embolectomy devices showed better recanalization rates with the newer devices[31,32]. However, trials comparing the use of newer devices to no embolectomy are lacking.

One RCT enrolling 118 examined the effect of thrombectomy compared to no thrombectomy[30]. The effect of mechanical thrombectomy on mortality (OR 0.3; 95% CI 0.3 to 1.76) and functional outcome (OR 0.90; 95% CI 0.36 to 2.25) remains uncertain. The quality of evidence was low due to indirectness and imprecision for mortality and good functional outcomes [Table 7].

*Implementation:*
The feasibility of implementing this intervention varies according to the centers. Only few centers in KSA are equipped to provide this intervention. Barriers include availability of trained healthcare providers, equipment and stroke units.

**Recommendation 6:**

The Ministry of Health of Saudi Arabia panel suggests against using mechanical thrombectomy in the management of patients with acute ischemic stroke. (Weak recommendation, low quality of evidence).

*Remark:*
Some carefully selected patients who value the uncertain benefits of mechanical thrombectomy more than the associated risk may choose this intervention.

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# Appendices

1. Search Strategies and Results
2. Summary of Findings and Evidence-to-Recommendation Tables

**Appendix 1: Search Strategies and Results**

| Databases: Medline and Cochrane Library | |
|---|---|
| Search strategy: | Date of search: 2013-10-19 |

1. exp Intracranial Hemorrhages/
2. exp *Brain Ischemia/
3. exp *"intracranial embolism and thrombosis"/ or exp *intracranial hemorrhages/ or exp *stroke/ or exp *brain infarction/
4. exp *Heparin/ or exp *Heparin, Low-Molecular-Weight/
5. exp *Stockings, Compression/
6. exp *Heparinoids/
7. exp *embolectomy/ or exp *thrombectomy/
8. intermittent Pneumatic Compression Stockings.mp.
9. *Fibrinolytic Agents/tu [Therapeutic Use]
10. *Thrombolytic Therapy/mt [Methods]
11. *Tissue Plasminogen Activator/tu [Therapeutic Use]
12. bandages/ or stockings, compression/
13. exp Anticoagulants/
14. Intermittent Pneumatic Compression Devices/
15. 1 or 2 or 3
16. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
17. 15 and 16
18. limit 17 to (english language and humans and yr="2012 -Current")
19. (MEDLINE or metaanaly$ or meta-analy$ or (systemat$ adj10 review$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
20. limit 18 to (case reports or clinical conference or comment or congresses or editorial or in vitro or letter)
21. 18 not 20
22. 21 and 19
23. randomised controlled trial.pt.
24. controlled clinical trial.pt.
25. random$.ab.
26. trial.ab.
27. groups.ab.
28. 23 or 24 or 25 or 26 or 27
29. 21 and 28

Date: 2012 – 2013-10-19

**Summary of Searches**

| | |
|---|---|
| **Total No. Retrieved:** | 727 |
| Cochrane: | 330 |
| Medline: | 397 |
| **Screening** (Title and Abstract Review) | |
| No. Excluded: | 714 |
| Included for Full Text review: | 13 |
| **Selection** (Full Text Review) | |
| No. Excluded: | 10 |
| Reasons for exclusions: | |
| 1. Different intervention<br>2. Different comparator<br>3. Protocol | |
| **No. Selected:** | 3 |
| 1. RCT (2)<br>2. SR (1) | |

## Appendix 2: Summary of Findings and Evidence-to-Recommendation Tables

### Table 2
### Summary of Findings: IV r-tPA Initiated Within 3 h in Patients with Acute Ischemic Stroke

**IV t-PA compared to no IV t-PA for acute ischemic stroke with symptoms onset < 3 hours**

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | | | | |
| | **Risk with No IV t-PA** | **Risk difference with IV t-PA** | | | |
| **Mortality** | **120 deaths per 1000** | **10 fewer deaths per 1000** (from 29 fewer to 14 more) | **OR 0.91** (0.73 to 1.13)[1] | 1806 (7 studies[2]) 90 days | ⨁⨁⨁⨁ **HIGH**[3,4] |
| **Good functional outcome, mRS 0-1**[5] | **317 good outcomes per 1000** | **98 more good outcomes per 1000** (from 52 more to 146 more) | **OR 1.53** (1.26 to 1.86)[6] | 1806 (7 studies[2]) 90 days | ⨁⨁⨁⨁ **HIGH**[5,7] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Although the upper limit of CI included a 13% relative risk (1.4% absolute risk) increase in risk of death, this was not judged to be of low impact in the face of large benefit. We did not downgrade for imprecision.
[2] Haley 1993, NINDS 1995, ECASS 1995, ECASS 1998, ATLANTIS 1999, ATLANTIS 2000, IST III 2013
[3] Allocation unclear in two studies
[4] $I^2$=0%
[5] in the IST III good functional outcome was defined oxford handicap score 0 - 2 which is very similar to mRS, we did not downgrade for indirectness
[6] Calculated based on total number of mRS 0-1 or OHS 0-1 in all trials combined, because the number for individual trials on this outcome were not available for this time window
[7] We did not have data from individual studies, so data were combined from meta-analysis (Lancet 2013) and we could not assess for heterogeneity.

**Table 3**
**Summary of Findings: IV r-tPA Initiated Within 3 to 4.5 h in Patients with Acute Ischemic Stroke**

**IV r-tPA compared to no IV r-tPA for patients with ischemic stroke within 3 to 4.5 hours of symptom onset**

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk | | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | **Risk with No IV-tPA** | **Risk difference with IV t-PA** | | | |
| **Mortality** | **120 deaths per 1000** | **23 more per 1000** (from 14 fewer to 69 more) | **RR 1.22** (0.87 to 1.71)[1] | 1620 (5 studies[5]) 90 days | ⨁⨁◯◯ **LOW**[2,3] due to inconsistency, imprecision |
| **Good functional outcome, mRS of 0 or 1** | **350 good outcomes per 1000** | **69 more per 1000** (from 13 more to 125 more) | **RR 1.34** (1.06 to 1.68) | 1620 (5 studies[5]) 90 days | ⨁⨁⨁⨁ **HIGH** |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] There is a significantly increased risk of fatal ICH associated with thrombolytic therapy across all time to treatment strata up to 6 hours OR= 3.70 [95% CI 2.36, 5.79 ]

[2] I-squared 70%

[3] Wide confidence intervals ranging from 0.78 - 1.39 on mortality

[4] Symptomatic non-fatal ICH more likely than placebo in the 3 - 6 hour time window. OR = 3.34; 95% CI 2.4 - 4.7. 8.4% vs. 2.5%.

[5] ATLANTIS, ECASS I (1995), ECASS II (1998), ECASS III (2008), and EPITHET.

**Table 4**
**Summary of Findings: IV r-tPA Initiated Within 4.5 to 6 h in Patients with Acute Ischemic Stroke**

**IV r-tPA compared to no IV r-tPA for patients with ischemic stroke within 4.5 to 6 hours of symptoms onset**

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk Risk with No IV tPA | Risk difference with IV t-PA | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| **Mortality**[7] | **120 deaths per 1000** | **49 more per 1000** (from 0 more to 112 more)[1] | **OR 1.49** (1 to 2.21)[2] | 1117 (4 studies[3]) | ⊕⊕⊕◯ **MODERATE**[4] due to imprecision |
| **Good functional outcome, mRS 0-1**[8] | **350 good outcomes per 1000** | **46 more per 1000** (from 9 fewer to 103 more)[5] | **OR 1.22** (0.96 to 1.54)[2] | 1117 (4 studies[3]) 90 days | ⊕⊕⊕◯ **MODERATE**[6] due to imprecision |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Baseline mortality rate (217 of 1,822 5 11.9%) derived from placebo arms of r-tPA trial (NINDS, ECASS, ATLANTIS, and EPITHET).

[2] This is an adjusted OR that takes differences in baseline NIHSS score, age, and BP into account.

[3] ATLANTIS A (2000), ECASS I (1995), ECASS II (1998), and EPITHET.

[4] Rated down for imprecision because recommendation would be in favor of r-tPA if the effect of r-tPA matched the lower bound of the CI (i.e., OR = 1 indicating no effect on mortality).

[5] Baseline good functional outcome percentage (641 of 1,822 = 35.2%) derived from placebo arms of r-tPA trials (NINDS, ECASS, ATLANTIS, and EPITHET).

[6] CI includes the possibility of harm and benefit.

[7] Fatal ICH not reported separately because it is captured in overall mortality. There is a significantly increased risk of fatal ICH associated with thrombolytic therapy across all time-to-treatment strata up to 6 h; OR = 3.70 (95% CI, 2.36-5.79). Absolute risks are 3.5% with r-tPA and 0.8% with placebo; seven studies.

[8] Symptomatic nonfatal ICH not reported separately in table as it is captured by good functional outcome. Symptomatic nonfatal ICH more likely than placebo in the 3-6-h time window. OR = 3.34; 95% CI, 2.4-4.7; 8.4% vs 2.5%, six studies (three ECASS trials, two ATLANTIS trials, and EPITHET 2008). Data from Wardlaw et al.

**Table 5**
**Summary of Findings: IA r-tPA in Patients with Acute Ischemic Stroke**

**IA thrombolysis compared to no IA thrombolysis for patients with acute ischemic stroke**

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk | | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with No IA t-PA | Risk difference with IA t-PA | | | |
| **Mortality** | **210 deaths per 1000**[1] | **29 fewer per 1000** (from 92 fewer to 69 more) | **RR 0.86** (0.56 to 1.33) | 334 (3 studies[2]) 90 days | ⨁⨁◯◯ **LOW**[3,4] due to indirectness, imprecision |
| **Good functional outcome, mRS 0-2** | **290 good outcomes per 1000**[5] | **128 more per 1000** (from 17 more to 275 more) | **RR 1.44** (1.06 to 1.95) | 334 (3 studies) 90 days | ⨁⨁⨁◯ **MODERATE**[3] due to indirectness |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Baseline mortality rate derived from mortality in control and treatment arms of PROACT I (1998), PROACT II (1999), MELT (2007), and the control arm of NINDS (1995) as reported in the IMS (2004) study (153 of 727 = 21%). Intervention and control rates were averaged to determine the baseline rate, because the interventions did not have a notable effect on mortality.
[2] PROACT I (1998), PROACT II (1999), MELT (2007).
[3] Studies conducted in patients without contraindication for IV r-tPA; studies used thrombolytics other than r-tPA; control patients received heparin in PROACT I (1998) and PROACT II (1999).
[4] CI includes both clinically significant harms and benefits.
[5] Baseline good functional outcome rate derived from control arms of PROACT I (1998) and PROACT II (1999), MELT (2007), and the control arm of NINDS as reported in the IMS study (99 of 341 = 29%).

**Table 6**
**Summary of Findings: IA and IV r-tPA in Patients with Acute Ischemic Stroke**

**Combination of IV and IA r-tPA compared to IV r-tPA alone for acute ischemic stroke**

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk | | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | **Risk with IV r-tPA alone** | **Risk difference with Combination of IV and IA r-tPA** | | | |
| **Mortality** | **210 deaths per 1000**[1] | **48 fewer per 1000** (from 107 fewer to 46 more) | **RR 0.77** (0.49 to 1.22)[2] | 343 (2 studies[2]) 90 d | ⊕⊖⊖⊖ **Very Low**[3] due to risk of bias, imprecision |
| **Good functional outcomes, mRS 0-2** | **290 good outcomes per 1000**[2] | **38 more per 1000** (from 35 fewer to 131 more) | **RR 1.13** (0.88 to 1.45)[2] | 343 (2 studies[2]) 90 d | ⊕⊖⊖⊖ **Very Low**[3] due to risk of bias, imprecision |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Baseline mortality rate derived from mortality in control and treatment arms of PROACT I (1998), PROACT II (1999), MELT (2007), and the placebo and control arms of NINDS (1995) as reported in the IMS (2004) study (153 of 727 = 21%). Intervention and control rates were averaged to determine the baseline rate, because the interventions did not have notable effect on mortality.

[2] IMS I (2004) and IMS II (2007). Both studies used the same historical data for their control groups. Historical controls were obtained from the active treatment arm of the NINDS (1995) tPA trial. Control population was limited to patients with baseline NIHSS. 9 and age, 81 y to match the IMS cohorts. We thus combined data from the two studies for the intervention group and compared with the data from the same historical control group. Baseline Good Functional Outcome rate derived from control arms of PROACT I (1998) and PROACT II (1999), MELT (2007) and the placebo control arms of NINDS as reported in the IMS study (99 of 341 5 29%).

[3] CI includes both values indicating harms and benefit.

[4] Major extracranial bleeding not reported as separate outcome because it is captured in the other listed outcomes. Major extracranial bleeding occurred in 2.5% of IV 1 IA-treated patients and 1.1% of IV tPA alone-treated patients (RR, 2.3; 95% CI, 0.4-12.1).

[5] sICH not reported as separate outcome because it is captured in the other listed outcomes. sICH occurred in 13 of 161 patients (8.0%) treated with combined IV 1 IA tPA and in 12 of 182 patients (6.6%) treated with IV tPA alone (RR, 1.23; 95% CI, 0.58-2.57).

**Table 7**
**Summary of Findings: Mechanical Thrombectomy in Patients with Acute Ischemic Stroke**

**Mechanical Thrombectomy compared to No Mechanical Thrombectomy for acute ischemic stroke**

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk | | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with medical therapy | Risk difference with Thrombectomy | | | |
| **Mortality** | **210 deaths per 1000** | **53 fewer deaths per 1000** (from 153 fewer to 117 more) | **OR 0.73** (0.30 to 1.76)[4] | 118 (1 study[1]) 90 days | ⨁⨁◯◯ **LOW**[2,3] due to indirectness, imprecision |
| **Good functional outcome, mRS 0-2** | **290 good outcomes per 1000** | **16 fewer good outcomes per 1000** (from 117 fewer to 160 more) | **OR 0.90** (0.36 to 2.25)[4,5] | 118 (1 study[1]) 90 days | ⨁⨁◯◯ **LOW**[2,3] due to indirectness, imprecision |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Kidwell et al. (MR RESCUE); other studies were not included due to use of different control group (IMS III), or lack of subgroup data (SYNTHESIS Expansion).
[2] IV r-tPA was used in both groups prior to randomization, 28 of 64 (43%) in the thrombectomy group, and 16 of 54 (29.6%) in the standard medical therapy group. Hence we lowered for indirectness.
[3] Wide CI that included significant harm and significant benefit
[4] Data from Kidwell et al.
[5] Symptomatic ICH developed in 3 patients out of 64 (4.7%) in the thrombectomy group and 2 out of 52 patients in the control group (OR1.22; 95% CI 0.21 to 7.02)

**Evidence to recommendation framework 1**

## Guideline Question: Should IV r-tPA be used in patients with acute ischemic stroke presenting within 3 hours of symptoms onset?

***Problem:*** Adult patients with acute ischemic stroke presenting within 3 hours of symptoms onset
***Option:*** IV r-tPA
***Comparison:*** No r-tPA
***Setting:*** Hospital
***Perspective:*** Individual decision making

***Background:*** Stroke is a common disease that is associated with significant morbidity and mortality. A single center study in KSA showed a prevalence of stroke to be 29 per 100,000 per year; larger and methodologically sound studies are required to accurately describe the prevalence of stroke in KSA. Although the burden of stroke on health care system in KSA appears to be large, there are no data to quantify the impact on patients, policy makers and health care providers.
Reperfusion of ischemic brain tissue may be achieved with the use of thrombolytic therapy. Recombinant tissue plasminogen activator (r-tPA) is used widely to treat patients presenting with acute ischemic stroke, however there is variation in the safety and efficacy of this intervention that depends on multiple factors.

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ | See table below | Although no available studies to inform the baseline risk of outcomes in patients with acute ischemic stroke, the risk is probably similar to what is available in literature from other regions in the world. |

| Outcome | Assumed Baseline Risk in Systematic Review | Adult patients with stroke in Saudi Arabia |
|---|---|---|
| Mortality | 120 per 1000 | No epidemiologic studies in the context of Saudi Arabia |
| Good functional outcome | 317 per 1000 | No epidemiologic studies in the context of Saudi Arabia |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| BENEFITS & HARMS OF THE OPTIONS | **What is the overall certainty of this evidence?** | ☐ No included studies ☐ Very low ☐ Low ☐ Moderate ☒ High | ***The relative importance or values of the main outcomes of interest:*** | For Mortality outcome: the CI (0.73 to 1.13) contain significant benefit and potential harm (13% relative risk increase or 14 more deaths per 1000 treated patients) the MOH KSA panel members felt that this is not a significant risk that would result in downgrading the quality of evidence. i.e. the magnitude of risk would be acceptable in the face of large benefit observed in othe critical outcomes. |
| | **Is there important uncertainty about how much people value the main outcomes?** | ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☒ No known undesirable outcomes | ***Summary of the evidence for patients' values and preferences:*** Six studies were identified in the systematic review used for the AT9 guidelines, we did not identify any new studies. None of the published studies target the KSA population. Individuals who experienced an event, may associate a higher utility to that event compared to those who did not experience the same event.. This factor may be important to consider when eliciting health state valuations for outcomes associated with antithrombotic treatment. Studies also illustrate that other factors such as severity of stroke, sex, age, and living conditions affect the willingness to accept or refuse treatment options. One study suggested that The most significant reason for accepting treatment was the desire to maintain functional independence. | No studies were identified that reflect on values and preferences in the context of Saudi Arabia. Evidence was considered from systematic used for the AT9 guidelines. |
| | **Are the desirable anticipated effects large?** | ☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies | | |
| | **Are the undesirable anticipated effects small?** | ☐ No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ Varies | | Fatal ICH not reported separately because it is captured in overall mortality. There is a significantly increased risk of fatal ICH associated with thrombolytic therapy across all time-to-treatment strata up to 6 h, OR = 3.70 (95% CI, 2.36-5.79). Absolute risks are 3.5% with r-tPA and 0.8% with placebo. Symptomatic nonfatal ICH not reported separately because this outcome is |

| Outcome | Relative importance | Certainty of the evidence |
|---|---|---|
| *Mortality* | Critical | High |
| *Good functional out-comes** | Critical | High |

**** good functional outcome is defined as modified Rankin score (mRS 0 -1), or a Oxford handicap score 0 -2.***

**Reference:**

MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2)(suppl):e1S-e23S.

***Summary of the evidence for the relative effect of interventions*:** Please

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| | | | see evidence table and reference list.<br>The high quality evidence showing an absolute increase in good functional outcomes with r-tPA use was judged to be larger than the uncertainty around mortality outcome. In the worst case scenario r-tPA use will result in 14 more deaths compared to 52 more good outcomes, the panel members judged that the overall benefit outweighs the risk. | captured under good functional outcome. Symptomatic nonfatal ICH more likely with r-tPA (8.6%) than placebo (1.5%). OR = 4.28; 95% CI, 2.4-7.8. |
| | **Are the desirable effects large relative to undesirable effects?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ \| ***Varies*** ☐ | | See the summary of findings table |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | **Are the resources required small?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | No evidence identified in the context of Saudi Arabia | The MOH KSA panel members felt that resources are available. However, there are some barriers. See remarks below. |
| | **Is the incremental cost small relative to the net benefits?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ \| ***Varies*** ☐ | No data in the context of Saudi Arabia.<br><br>Literature search identified a recent cost effectiveness review on medical therapies for acute stroke, this review summarized seven cost effectiveness studies on r-tPA use within 3 hours. We summarize the data qualitatively: the use of r-tPA is the most cost effective option for acute stroke treatment especially for long term outcomes.<br>One study suggested that r-tPA use resulted in additional 3.46 QALY per patient with average cost savings of $3800 per patient.<br>Another study showed that at 12 months ICER of rtPA within 3 hours is 13,581 pounds per QALY gained.<br>Another study showed that rtPA saves $6074 and adds 0.75 QALY per use.<br><br>**Reference**:<br>Pan F; Hernandez L; Ward A. Cost-effectiveness of stroke treatment and secondary preventions. Expert Opin Pharmacother. 2012;13(12):1751-1760 | Panel members agreed that it is likely that the use of r-tPA within 3 hours is cost effective in the context of Saudi Arabia, and that we can extrapolate from available literature. |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| EQUITY | What would be the impact on health inequities? | Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☒ / Reduced ☐ / Varies ☐ | None | There is a large burden of the disease in Saudi Arabia, and likely this intervention will result in reducing health inequity if implemented widely in the Kingdom of Saudi Arabia. |
| ACCEPTABILITY | Is the option acceptable to key stakeholders ? | No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐ | None | Considering different stakeholders including patients, clinicians, and policymakers; the KSA MOH panel members felt that this is probably acceptable. Factors that could affect acceptability include availability of radiologists, workload, working hours, lack of appropriate incentives. |
| FEASIBILITY | Is the option feasible to implement? | No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☒ | None | Panel members agreed that it is feasible to create stroke units and to provide the intervention in well-equipped centres. However, there is a large variation between regions and health care facilities in Saudi Arabia that could be a barrier for implementation. Barriers include: availability of machine (i.e. CT scan), workload and working hours, pre-hospital transportation. They suggested centralizing stroke centers in each region to overcome these barriers and to provide incentives. |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☐ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☐ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option ☐ | We suggest not offering this option ☐ | We suggest offering this option ☐ | We recommend offering this option ☒ |

| | |
|---|---|
| **Recommendation (text)** | KSA Ministry of Health panel members **recommend using** IV r-tPA in patients with acute ischemic stroke and symptoms onset less than 3 hours over no IV r-tPA. |
| **Justification** | High quality of evidence for benefit, treatment appear to be cost effective, acceptability of the intervention, and feasibility of implementation |
| **Subgroup considerations** | No special subgroups to consider |
| **Implementation considerations** | The following suggestions to enhance implementation:<br>Public awareness using media and education about this health condition and available interventions<br>Providing resources to facilitate implementation<br>May consider referring to available implementation tools from other organizations/countries |
| **Monitoring and evaluation** | Quality measurement include recording the number of centers providing the intervention, mortality and disability, other factors that need to be identified before implementing the treatment (e.g. door to needle time and ICU).<br>Suggestion to refer to international quality measures |
| **Research priorities** | National stroke registry to help inform future guidelines about demographics and prevalence of the disease.<br>Surveys to study values and preferences of patients in KSA.<br>Cost-effectiveness studies in the context of KSA |

## Summary of findings table

**Author(s):** Alhazzani W

**Date:** 2013-11-27

**IV t-PA compared to no IV t-PA for acute ischemic stroke with symptoms onset < 3 hours**

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | | | | |
| | Risk with No IV t-PA | Risk difference with IV t-PA | | | |
| **Mortality** | **120 deaths per 1000** | **10 fewer deaths per 1000** (from 29 fewer to 14 more) | **OR 0.91** (0.73 to 1.13)[1] | 1806 (7 studies[2]) 90 days | ⨁⨁⨁⨁ **HIGH**[3,4] |
| **Good functional outcome, mRS 0-1**[5] | **317 good outcomes per 1000** | **98 more good outcomes per 1000** (from 52 more to 146 more) | **OR 1.53** (1.26 to 1.86)[6] | 1806 (7 studies[2]) 90 days | ⨁⨁⨁⨁ **HIGH**[5,7] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Although the upper limit of CI included a 13% relative risk (1.4% absolute risk) increase in risk of death, this was not judged to be of low impact in the face of large benefit. We did not downgrade for imprecision.
[2] Haley 1993, NINDS 1995, ECASS 1995, ECASS 1998, ATLANTIS 1999, ATLANTIS 2000, IST III 2013
[3] Allocation unclear in two studies
[4] $I^2$=0%
[5] in the IST III good functional outcome was defined oxford handicap score 0 - 2 which is very similar to mRS, we did not downgrade for indirectness
[6] Calculated based on total number of mRS 0-1 or OHS 0-1 in all trials combined, because the number for individual trials on this outcome were not available for this time window
[7] We did not have data from individual studies, so data were combined from meta-analysis (Lancet 2013) and we could not assess for heterogeneity.

**References**

**Systematic Review**

1. Wardlaw J, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 2012; 379: 2364–72.

**RCTs:**

1. Haley EC Jr, Brott TG, Sheppard GL, et al. Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke. The TPA Bridging Study Group. *Stroke* 1993; 24: 1000‑04.
2. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischaemic stroke. N Engl J Med 1995; 333: 1581–87.
3. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA 1995; 274: 1017–25.
4. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998; 352: 1245–51.
5. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0– to 6–hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Thrombolytic therapy in acute ischemic stroke study investigators. Stroke 2000; 31: 811–16.
6. Albers GW, Clark WM, Madden KP, Hamilton SA. ATLANTIS trial: results for patients treated within 3 hours of stroke onset. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. Stroke 2002; 33: 493–95.
7. The IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet 2012; published online May 23. DOI: 10.1016/S0140-6736(12)60768-5.

**Evidence to recommendation framework 2**

## Guideline Question: Should IV r-tPA be used in patients with acute ischemic stroke presenting 3 to 4.5 hours of symptoms onset?

***Problem:*** Adult patients with acute ischemic stroke presenting within 3 to 4.5 hours of symptoms onset
***Option:*** IV r-tPA
***Comparison:*** No r-tPA
***Setting:*** Hospital
***Perspective:*** Individual decision making

***Background:*** Stroke is a common disease that is associated with significant morbidity and mortality. A single center study in KSA showed a prevalence of stroke to be 29 per 100,000 per year; larger and methodologically sound studies are required to accurately describe the prevalence of stroke in KSA. Although the burden of stroke on health care system in KSA appears to be large, there are no data to quantify the impact on patients, policy makers and health care providers.
Reperfusion of ischemic brain tissue may be achieved with the use of thrombolytic therapy. Recombinant tissue plasminogen activator (r-tPA) is used widely to treat patients presenting with acute ischemic stroke, however there is variation in the safety and efficacy of this intervention that depends on multiple factors.

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ | See table below | Although no available studies to inform the baseline risk of outcomes in patients with acute ischemic stroke, the risk is probably similar to what is available in literature from other regions in the world. |

| Outcome | Assumed Baseline Risk in Systematic Review | Adult patients with stroke in Saudi Arabia |
|---|---|---|
| Mortality | 120 per 1000 | No epidemiologic studies in the context of Saudi Arabia |
| Good functional outcome | 317 per 1000 | No epidemiologic studies in the context of Saudi Arabia |

BENEFITS & HARMS OF THE OPTIONS

| CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|
| **What is the overall certainty of this evidence?** | *No included studies* ☐ \| *Very low* ☐ \| *Low* ☒ \| *Moderate* ☐ \| *High* ☐ | ***The relative importance or values of the main outcomes of interest:*** | |
| **Is there important uncertainty about how much people value the main outcomes?** | *Important uncertainty or variability* ☐ \| *Possibly important uncertainty or variability* ☐ \| *Probably no important uncertainty or variability* ☐ \| *No important uncertainty or variability* ☐ \| *No known undesirable outcomes* ☒ | ***Summary of the evidence for patients' values and preferences:*** Six studies were identified in the systematic review used for the AT9 guidelines, we did not identify any new studies. None of the published studies target the KSA population. Individuals who experienced a given health event, may associate a higher utility to that event compared to those who did not experience the event . This factor may be important to consider when eliciting health state valuations for outcomes associated with antithrombotic treatment. Studies also illustrate that other factors such as severity of stroke, age, sex, and living situation affect willingness to accept or reject treatment options. One study suggested that The most significant reason for accepting treatment was the desire to maintain functional independence. | No studies were identified that reflect on values and preferences in the context of Saudi Arabia. Evidence was considered from systematic review used for the AT9 guidelines. |
| **Are the desirable anticipated effects large?** | *No* ☐ \| *Probably No* ☐ \| *Uncertain* ☐ \| *Probably Yes* ☐ \| *Yes* ☒ \| ***Varies*** ☐ | | |
| **Are the undesirable anticipated effects small?** | *No* ☐ \| *Probably No* ☐ \| *Uncertain* ☐ \| *Probably Yes* ☒ \| *Yes* ☐ \| ***Varies*** ☐ | ***Summary of the evidence for the relative effect of interventions*:** | Fatal ICH not reported separately because it is captured in overall mortality. There is a significantly increased risk of fatal ICH associated with thrombolytic therapy across all time-to-treatment strata up to 6 h, OR = 3.70 (95% CI, 2.36-5.79). Absolute risks are 3.5% with tPA and 0.8% with placebo. Symptomatic nonfatal ICH not reported separately because this outcome is captured under good functional outcome. Symptomatic nonfatal ICH more likely with tPA (8%) than placebo (1.2%). OR = |

| Outcome | Relative importance | Certainty of the evidence |
|---|---|---|
| *Mortality* | Critical | Low |
| *Good functional outcomes** | Critical | High |

**** good functional outcome is defined as modified Rankin score (mRS 0 -1), or a Oxford handicap score 0 -2.***

**Reference:**

MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2)(suppl):e1S-e23S.

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| | | | Please see evidence table and reference list. | 4.55; 95% CI, 2.3-7.1. |
| | **Are the desirable effects large relative to undesirable effects?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ | | See the summary of findings table |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | **Are the resources required small?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | No evidence identified | |
| | **Is the incremental cost small relative to the net benefits?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ | No data available on cost effectiveness in Saudi Arabia context.<br><br>In a hypothetical cohort r-tPA resulted in a gain of 0.77 years of life (95% credible range 0.0005 to 0.17) and 0.24 quality-adjusted life-years (95% credible range 0.01 to 0.60) and a difference in cost of $1,495 (95% credible range –$4,637 to $6,100) compared with placebo. r-tPA was cost-effective, especially in younger patients and those with higher National Institutes of Health Stroke Scale scores, but not cost-effective in those with diabetes or atrial fibrillation.<br><br>Another study suggested that the administration of r-tPA compared with standard medical therapy resulted in a lifetime gain of 0.28 QALYs for an additional cost of $6050, yielding an incremental cost-effectiveness ratio (ICER) of $21 978 per QALY<br><br>**References**:<br>1. Boudreau D; Guzauskas G; Villa F; et al. A Model of Cost-effectiveness of Tissue Plasminogen Activator in Patient Subgroups 3 to 4.5 Hours After Onset of Acute Ischemic Stroke. Ann Emerg Med. 2013;61:46-55<br>2. Tung C; Win S; Lansberg M. Cost-Effectiveness of Tissue-Type Plasminogen Activator in the 3- to 4.5-Hour Time Window for Acute Ischemic Stroke. Stroke. 2011;42:2257-2262. | Panel members agreed that it is likely that the use of r-tPA within 3 to 4.5 hours may be cost effective in the context of Saudi Arabia, and that we can extrapolate from available literature. |
| EQUITY | **What would be the impact on health inequities?** | *Increased* ☐ *Probably increased* ☐ *Uncertain* ☐ *Probably reduced* ☒ *Reduced* ☐ ***Varies*** ☐ | None | There is a large burden of the disease in Saudi Arabia, and likely this intervention will result in reducing health inequity if implemented widely in the Kingdom of Saudi Arabia. |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| ACCEPTABILITY | **Is the option acceptable to key stakeholders ?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | None | Considering different stakeholders including patients, clinicians, and policymakers; the KSA MOH panel members felt that this is probably acceptable. Factors that could affect acceptability include availability of radiologists, workload, working hours, lack of appropriate incentives. |
| FEASIBILITY | **Is the option feasible to implement?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☒ | None | Panel members agreed that it is feasible to create stroke units and to provide the intervention in well-equipped centres. However, there is a large variation between regions and health care facilities in Saudi Arabia that could be a barrier for implementation. Barriers include: availability of machine (i.e. CT scan), workload and working hours, pre-hospital transportation. They suggested centralizing stroke centers in each region to overcome these barriers and to provide incentives. |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☐ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☒ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option ☐ | We suggest not offering this option ☐ | We suggest offering this option ☒ | We recommend offering this option ☐ |

| | |
|---|---|
| **Recommendation (text)** | KSA MoH panel members **suggest** using of IV r-tPA in patients with acute ischemic stroke presenting between 3 to 4.5 hours, over no IV r-tPA. |
| **Justification** | Low quality of evidence supports the desirable over undesirable effects, intervention is probably cost effective, acceptable and feasible to implement, with no variation in patients values and preferences. |
| **Subgroup considerations** | Although diabetic patients and elderly patients were excluded from one large RCT, there are no subgroup analyses to inform decision making in elderly patients or patients with diabetes. The panel members think that generalizability of the observed effect to this population is reasonable. |
| **Implementation considerations** | The following suggestions to enhance implementation:<br>Public awareness using media and education about this health condition and available interventions<br>Providing resources to facilitate implementation<br>May consider referring to available implementation tools from other organizations/countries |
| **Monitoring and evaluation** | Quality measurement include records of centers providing the intervention, mortality and disability, other factors that need to be identified before implementing the treatment (e.g. door to needle time and ICU).<br>Suggestion to refer to international quality measures |
| **Research priorities** | National stroke registry to help inform future guidelines about demographics and prevalence of the disease.<br>Surveys to study values and preferences of patients in KSA.<br>Cost-effectiveness studies in the context of KSA |

## Summary of findings table

**Author(s):** Alhazzani W
**Date:** 2013-11-27

### IV r-tPA compared to no IV r-tPA for patients with ischemic stroke within 3 to 4.5 hours of symptom onset

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk | | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | **Risk with No IV-tPA** | **Risk difference with IV t-PA** | | | |
| **Mortality** | **120 deaths per 1000** | **23 more per 1000** (from 14 fewer to 69 more) | **RR 1.22** (0.87 to 1.71)[1] | 1620 (5 studies[5]) 90 days | ⨁⨁◯◯ **LOW**[2,3] due to inconsistency, imprecision |
| **Good functional outcome, mRS of 0 or 1** | **350 good outcomes per 1000** | **69 more per 1000** (from 13 more to 125 more) | **RR 1.34** (1.06 to 1.68) | 1620 (5 studies[5]) 90 days | ⨁⨁⨁⨁ **HIGH** |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] There is a significantly increased risk of fatal ICH associated with thrombolytic therapy across all time to treatment strata up to 6 hours OR= 3.70 [95% CI 2.36, 5.79 ]

[2] I-squared 70%

[3] Wide confidence intervals ranging from 0.78 - 1.39 on mortality

[4] Symptomatic non-fatal ICH more likely than placebo in the 3 - 6 hour time window. OR = 3.34; 95% CI 2.4 - 4.7. 8.4% vs. 2.5%.

[5] ATLANTIS, ECASS I (1995), ECASS II (1998), ECASS III (2008), and EPITHET.

**References**

**Systematic Reviews:**

1. Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2009 ;( 4): CD000213.
2. Lees KR , Bluhmki E , von Kummer R , et al ; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group . Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials . *Lancet* . 2010 ; 375 ( 9727 ): 1695 - 1703 .

**Randomized Trials:**

1. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA 1995; 274: 1017–25.
2. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998; 352: 1245–51.
3. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4·5 hours after acute ischemic stroke. N Engl J Med 2008; 359: 1317–29.
4. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0– to 6–hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Thrombolytic therapy in acute ischemic stroke study investigators. Stroke 2000; 31: 811–16.
5. Davis SM, Donnan G, Parsons MW, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol 2008; 7: 299–309.

**Evidence to recommendation framework 3**

## Guideline Question: Should IV r-tPA be used in patients with acute ischemic stroke presenting 4.5 to 6 hours of symptoms onset?

***Problem:*** Adult patients with acute ischemic stroke presenting after 4.5 to 6 hours of symptoms onset
***Option:*** IV r-tPA
***Comparison:*** No r-tPA
***Setting:*** Hospital
***Perspective:*** Individual decision making/health policy making

***Background:*** Stroke is a common disease that is associated with significant morbidity and mortality. A single center study in KSA showed a prevalence of stroke to be 29 per 100,000 per year; larger and methodologically sound studies are required to accurately describe the prevalence of stroke in KSA. Although the burden of stroke on health care system in KSA appears to be large, there are no data to quantify the impact on patients, policy makers and health care providers.
Reperfusion of ischemic brain tissue may be achieved with the use of thrombolytic therapy. Recombinant tissue plasminogen activator (r-tPA) is used widely to treat patients presenting with acute ischemic stroke, however there is variation in the safety and efficacy of this intervention that depends on multiple factors.

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐ | See table below | Although no available studies to inform the baseline risk of outcomes in patients with acute ischemic stroke, the risk is probably similar to what is available in literature from other regions in the world. |

| Outcome | Assumed Baseline Risk in Systematic Review | Adult patients with stroke in Saudi Arabia |
|---|---|---|
| Mortality | 120 per 1000 | No epidemiologic studies in the context of Saudi Arabia |
| Good functional outcome | 350 per 1000 | No epidemiologic studies in the context of Saudi Arabia |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| BENEFITS & HARMS OF THE OPTIONS | **What is the overall certainty of this evidence?** | No included studies ☐ \| Very low ☐ \| Low ☐ \| Moderate ☒ \| High ☐ | ***The relative importance or values of the main outcomes of interest:*** | |
| | **Is there important uncertainty about how much people value the main outcomes?** | Important uncertainty or variability ☐ \| Possibly important uncertainty or variability ☐ \| Probably no important uncertainty or variability ☐ \| No important uncertainty or variability ☐ \| No known undesirable outcomes ☒ | ***Summary of the evidence for patients' values and preferences:*** Six studies were identified in the systematic review used for the AT9 guidelines, we did not identify any new studies. None of the published studies target the KSA population. Individuals who experienced a given health event, may associate a higher utility to that event compared to those who did not experience the event . This factor may be important to consider when eliciting health state valuations for outcomes associated with antithrombotic treatment. Studies also illustrate that other factors such as severity of stroke, age, sex, and living situation affect willingness to accept or reject treatment options. One study suggested that The most significant reason for accepting treatment was the desire to maintain functional independence. | No studies were identified that reflect on values and preferences in the context of Saudi Arabia. Evidence was considered from systematic review used for the AT9 guidelines. |
| | **Are the desirable anticipated effects large?** | No ☐ \| Probably No ☒ \| Uncertain ☐ \| Probably Yes ☐ \| Yes ☐ \| ***Varies*** ☐ | | |
| | **Are the undesirable anticipated effects small?** | No ☒ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☐ \| Yes ☐ \| ***Varies*** ☐ | **Reference:** MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2)(suppl):e1S-e23S. ***Summary of the evidence for the relative effect of interventions*:** Please see evidence table and reference list. | Fatal ICH not reported separately because it is captured in overall mortality. There is a significantly increased risk of fatal ICH associated with thrombolytic therapy across all time-to-treatment strata up to 6 h, OR = 3.70 (95% CI, 2.36-5.79). Absolute risks are 3.5% with tPA and 0.8% with placebo. Symptomatic nonfatal ICH not reported separately because this outcome is captured under good functional outcome. Symptomatic nonfatal ICH more likely with tPA |

| Outcome | Relative importance | Certainty of the evidence |
|---|---|---|
| *Mortality* | Critical | Moderate |
| *Good functional outcomes** | Critical | Moderate |

**** good functional outcome is defined as modified Rankin score (mRS 0 -1), or a Oxford handicap score 0 -2.***

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| | | | | (8%) than placebo (1.2%). OR = 4.55; 95% CI, 2.3-7.1. |
| | **Are the desirable effects large relative to undesirable effects?** | *No* ☒ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ | | See the summary of findings table |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | Are the resources required small? | No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐ | No evidence identified | |
| | Is the incremental cost small relative to the net benefits? | No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐ | None | |
| EQUITY | What would be the impact on health inequities? | Increased ☒ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☐ / Varies ☐ | None | There is likely to be a low impact on health inequities. |
| ACCEPTABILITY | Is the option acceptable to key stakeholders ? | No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐ | None | |
| FEASIBILITY | Is the option feasible to implement? | No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐ | None | |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
| | ☒ | ☐ | ☐ | ☐ | ☐ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
| | ☒ | ☐ | ☐ | ☐ |

| | |
|---|---|
| **Recommendation (text)** | KSA MOH panel members **recommend not** using IV r-tPA in patients with acute ischemic stroke presenting between 4.5 to 6 hours of symptoms onset, over no IV r-tPA. |
| **Justification** | - |
| **Subgroup considerations** | None |
| **Implementation considerations** | - |
| **Monitoring and evaluation** | - |
| **Research priorities** | - |

## Summary of findings table

**Author(s):** Alhazzani W

**Date:** 2013-11-27

### IV r-tPA compared to no IV r-tPA for patients with ischemic stroke within 4.5 to 6 hours of symptoms onset

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk | | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | **Risk with No IV tPA** | **Risk difference with IV t-PA** | | | |
| **Mortality**[7] | **120 deaths per 1000** | **49 more per 1000** (from 0 more to 112 more)[1] | **OR 1.49** (1 to 2.21)[2] | 1117 (4 studies[3]) | ⊕⊕⊕◯ **MODERATE**[4] due to imprecision |
| **Good functional outcome, mRS 0-1**[8] | **350 good outcomes per 1000** | **46 more per 1000** (from 9 fewer to 103 more)[5] | **OR 1.22** (0.96 to 1.54)[2] | 1117 (4 studies[3]) 90 days | ⊕⊕⊕◯ **MODERATE**[6] due to imprecision |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Baseline mortality rate (217 of 1,822 5 11.9%) derived from placebo arms of r-tPA trial (NINDS, ECASS, ATLANTIS, and EPITHET).

[2] This is an adjusted OR that takes differences in baseline NIHSS score, age, and BP into account.

[3] ATLANTIS A (2000), ECASS I (1995), ECASS II (1998), and EPITHET.

[4] Rated down for imprecision because recommendation would be in favor of r-tPA if the effect of r-tPA matched the lower bound of the CI (i.e., OR = 1 indicating no effect on mortality).

[5] Baseline good functional outcome percentage (641 of 1,822 = 35.2%) derived from placebo arms of r-tPA trials (NINDS, ECASS, ATLANTIS, and EPITHET).

[6] CI includes the possibility of harm and benefit.

[7] Fatal ICH not reported separately because it is captured in overall mortality. There is a significantly increased risk of fatal ICH associated with thrombolytic therapy across all time-to-treatment strata up to 6 h; OR = 3.70 (95% CI, 2.36-5.79). Absolute risks are 3.5% with r-tPA and 0.8% with placebo; seven studies.

[8] Symptomatic nonfatal ICH not reported separately in table as it is captured by good functional outcome. Symptomatic nonfatal ICH more likely than placebo in the 3-6-h time window. OR = 3.34; 95% CI, 2.4-4.7; 8.4% vs 2.5%, six studies (three ECASS trials, two ATLANTIS trials, and EPITHET 2008). Data from Wardlaw et al.

**References**

**Systematic Reviews:**

1. Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2009 ;( 4): CD000213.
2. Lees KR , Bluhmki E , von Kummer R , et al ; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group . Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials . *Lancet* . 2010 ; 375 ( 9727 ): 1695 - 1703 .
3. Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet* 2012; 379: 2364–72.

**Randomized Trials:**

1. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA 1995; 274: 1017–25.
2. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998; 352: 1245–51.
3. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0– to 6–hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Thrombolytic therapy in acute ischemic stroke study investigators. Stroke 2000; 31: 811–16.
4. Davis SM, Donnan G, Parsons MW, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol 2008; 7: 299–309.

**Evidence to recommendation framework 4**

## Guideline Question: Should IA r-tPA be used in patients with acute ischemic stroke presenting within 6 hours of symptoms onset?

***Problem:*** Adult patients with acute ischemic stroke secondary to middle cerebral artery occlusion, presenting within 6 hours of symptoms onset
***Option:*** IA r-tPA
***Comparison:*** No r-tPA
***Setting:*** Hospital
***Perspective:*** Individual decision making

***Background:*** Stroke is a common disease that is associated with significant morbidity and mortality. A single center study in KSA showed a prevalence of stroke to be 29 per 100,000 per year; larger and methodologically sound studies are required to accurately describe the prevalence of stroke in KSA. Although the burden of stroke on health care system in KSA appears to be large, there are no data to quantify the impact on patients, policy makers and health care providers.
Reperfusion of ischemic brain tissue may be achieved with the use of thrombolytic therapy. Recombinant tissue plasminogen activator (r-tPA) is used widely to treat patients presenting with acute ischemic stroke, however there is variation in the safety and efficacy of this intervention that depends on multiple factors.

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐ | See table below | Although no available studies to inform the baseline risk of outcomes in patients with acute ischemic stroke, the risk is probably similar to what is available in literature from other regions in the world.<br>The risk is different in this population as it includes mainly patients with large artery occlusion (middle cerebral artery). |

| Outcome | Assumed Baseline Risk in Systematic Review | Adult patients with stroke in Saudi Arabia |
|---|---|---|
| Mortality | 210 per 1000 | No epidemiologic studies in the context of Saudi Arabia |
| Good functional outcome | 290 per 1000 | No epidemiologic studies in the context of Saudi Arabia |

BENEFITS & HARMS OF THE OPTIONS

| CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|
| **What is the overall certainty of this evidence?** | No included studies ☐ \| Very low ☐ \| Low ☒ \| Moderate ☐ \| High ☐ | ***The relative importance or values of the main outcomes of interest:*** | |
| **Is there important uncertainty about how much people value the main outcomes?** | Important uncertainty or variability ☐ \| Possibly important uncertainty or variability ☐ \| Probably no important uncertainty or variability ☐ \| No important uncertainty or variability ☐ \| No known undesirable outcomes ☒ | ***Summary of the evidence for patients' values and preferences:*** Six studies were identified in the systematic review used for the AT9 guidelines, we did not identify any new studies. None of the published studies target the KSA population. Individuals who experienced a given health event, may associate a higher utility to that event compared to those who did not experience the event . This factor may be important to consider when eliciting health state valuations for outcomes associated with antithrombotic treatment. Studies also illustrate that other factors such as severity of stroke, age, sex, and living situation affect willingness to accept or reject treatment options. One study suggested that The most significant reason for accepting treatment was the desire to maintain functional independence. | No studies were identified that reflect on values and preferences in the context of Saudi Arabia. Evidence was considered from systematic review used for the AT9 guidelines. |
| **Are the desirable anticipated effects large?** | No ☐ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☐ \| Yes ☒ \| ***Varies*** ☐ | | |
| **Are the undesirable anticipated effects small?** | No ☐ \| Probably No ☐ \| Uncertain ☒ \| Probably Yes ☐ \| Yes ☐ \| ***Varies*** ☐ | | The absolute effect of IA r-tPA on mortality ranged between absoulte reduction of 9.2 % to an absolute increase of 6.9%. Increased risk of symptomatic ICH (OR, 4.7; 95% CI, 1.3-16) |
| **Are the desirable effects large relative to undesirable effects?** | No ☐ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☒ \| Yes ☐ \| ***Varies*** ☐ | ***Summary of the evidence for the relative effect of interventions*:** Please see evidence table and reference list. | See the summary of findings table |

| Outcome | Relative importance | Certainty of the evidence |
|---|---|---|
| *Mortality* | Critical | Low |
| *Good functional outcomes** | Critical | Moderate |

**** good functional outcome is defined as modified Rankin score (mRS 0 -2)***

**Reference:**

MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2)(suppl):e1S-e23S.

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | Are the resources required small? | No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐ | No evidence identified | Setup for IA thrombolysis is not available in most centres in KSA. Both equipment and trained neurologists are required. |
| RESOURCE USE | Is the incremental cost small relative to the net benefits? | No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐ | None | |
| EQUITY | What would be the impact on health inequities? | Increased ☐ / Probably increased ☒ / Uncertain ☐ / Probably reduced ☐ / Reduced ☐ / Varies ☐ | None | Only few centers in KSA can provide this intervention, directing more resources to these centers will probably increase inequity. |
| ACCEPTABILITY | Is the option acceptable to key stakeholders ? | No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐ | None | The intervention may be acceptable for patients, some physicians. However, may not be that appealing for policymakers issues of cost, and the need for health professionals training. |
| FEASIBILITY | Is the option feasible to implement? | No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☒ | None | The feasibility is variable depending on the center and geographic location. |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☐ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☒ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option ☐ | We suggest not offering this option ☐ | We suggest offering this option ☒ | We recommend offering this option ☐ |

| | |
|---|---|
| **Recommendation (text)** | KSA MOH panel members **suggest** using IA r-tPA over no IA r-tPA, in patients with ischemic stroke due to large vessels occlusion who present after 4.5 hours of symptoms onset or don't meet eligibility criteria for IV r-tPA, provided that facilities and expertise are available. |
| **Justification** | - |
| **Subgroup considerations** | None |
| **Implementation considerations** | Provide training for neurologists<br>Availability of facilities<br>Centralization of treating centers |
| **Monitoring and evaluation** | No specific recommendation |
| **Research priorities** | National stroke registry to help inform future guidelines about demographics and prevalence of the disease.<br>Surveys to study values and preferences of patients in KSA.<br>Cost-effectiveness studies in the context of KSA |

## Summary of findings table

**Author(s):** Alhazzani W

**Date:** 2013-11-27

### IA thrombolysis compared to no IA thrombolysis for patients with acute ischemic stroke

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | | | | |
| | **Risk with No IA t-PA** | **Risk difference with IA t-PA** | | | |
| **Mortality** | **210 deaths per 1000**[1] | **29 fewer per 1000** (from 92 fewer to 69 more) | **RR 0.86** (0.56 to 1.33) | 334 (3 studies[2]) 90 days | ⨁⨁◯◯ **LOW**[3,4] due to indirectness, imprecision |
| **Good functional outcome, mRS 0-2** | **290 good outcomes per 1000**[5] | **128 more per 1000** (from 17 more to 275 more) | **RR 1.44** (1.06 to 1.95) | 334 (3 studies) 90 days | ⨁⨁⨁◯ **MODERATE**[3] due to indirectness |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Baseline mortality rate derived from mortality in control and treatment arms of PROACT I (1998), PROACT II (1999), MELT (2007), and the control arm of NINDS (1995) as reported in the IMS (2004) study (153 of 727 = 21%). Intervention and control rates were averaged to determine the baseline rate, because the interventions did not have a notable effect on mortality.
[2] PROACT I (1998), PROACT II (1999), MELT (2007).
[3] Studies conducted in patients without contraindication for IV r-tPA; studies used thrombolytics other than r-tPA; control patients received heparin in PROACT I (1998) and PROACT II (1999).
[4] CI includes both clinically significant harms and benefits.
[5] Baseline good functional outcome rate derived from control arms of PROACT I (1998) and PROACT II (1999), MELT (2007), and the control arm of NINDS as reported in the IMS study (99 of 341 = 29%).

**References**

**Systematic reviews:**

**1.** Fields JD, Khatri P, Nesbit GM, et al. Meta-analysis of randomized intra-arterial thrombolytic trials for the treatment of acute stroke due to middle cerebral artery occlusion. *Journal of neurointerventional surgery.* Jun 2011;3(2):151-155.

**Randomized Trials:**

1. Del Zoppo GJHR, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. Stroke. 1998; 29 (1): 4 - 11.
2. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA. 1999; 282 (21): 2003 - 2011.
3. Ogawa A, Mori E, Minematsu K, et al; MELT Japan Study Group. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fi brinolytic intervention trial (MELT) Japan. Stroke. 2007; 38 (10): 2633 - 2639.

**Evidence to recommendation framework 5**

## Guideline Question: Should the combination of IV & IA r-tPA be used in patients with acute ischemic stroke when compared to IV r-tPA alone?

***Problem:*** Adult patients with acute ischemic stroke
***Option:*** IA and IV r-tPA
***Comparison:*** IV r-tPA
***Setting:*** Hospital
***Perspective:*** Individual decision making/ Health system

***Background:*** Stroke is a common disease that is associated with significant morbidity and mortality. A single center study in KSA showed a prevalence of stroke to be 29 per 100,000 per year; larger and methodologically sound studies are required to accurately describe the prevalence of stroke in KSA. Although the burden of stroke on health care system in KSA appears to be large, there are no data to quantify the impact on patients, policy makers and health care providers.
Reperfusion of ischemic brain tissue may be achieved with the use of thrombolytic therapy. Recombinant tissue plasminogen activator (r-tPA) is used widely to treat patients presenting with acute ischemic stroke, however there is variation in the safety and efficacy of this intervention that depends on multiple factors.

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ | See table below | Although no available studies to inform the baseline risk of outcomes in patients with acute ischemic stroke, the risk is probably similar to what is available in literature from other regions in the world. |

| Outcome | Assumed Baseline Risk in Systematic Review | Adult patients with stroke in Saudi Arabia |
|---|---|---|
| Mortality | 210 per 1000 | No epidemiologic studies in the context of Saudi Arabia |
| Good functional outcome | 290 per 1000 | No epidemiologic studies in the context of Saudi Arabia |

BENEFITS & HARMS OF THE OPTIONS

| CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|
| **What is the overall certainty of this evidence?** | No included studies ☐ \| Very low ☐ \| Low ☒ \| Moderate ☐ \| High ☐ | ***The relative importance or values of the main outcomes of interest:*** | |
| **Is there important uncertainty about how much people value the main outcomes?** | Important uncertainty or variability ☐ \| Possibly important uncertainty or variability ☐ \| Probably no important uncertainty or variability ☐ \| No important uncertainty or variability ☐ \| No known undesirable outcomes ☒ | ***Summary of the evidence for patients' values and preferences:*** Six studies were identified in the systematic review used for the AT9 guidelines, we did not identify any new studies. None of the published studies target the KSA population. Individuals who experienced a given health event, may associate a higher utility to that event compared to those who did not experience the event . This factor may be important to consider when eliciting health state valuations for outcomes associated with antithrombotic treatment. Studies also illustrate that other factors such as severity of stroke, age, sex, and living situation affect willingness to accept or reject treatment options. One study suggested that The most significant reason for accepting treatment was the desire to maintain functional independence. | No studies were identified that reflect on values and preferences in the context of Saudi Arabia. Evidence was considered from systematic review used for the AT9 guidelines. |
| **Are the desirable anticipated effects large?** | No ☐ \| Probably No ☒ \| Uncertain ☐ \| Probably Yes ☐ \| Yes ☐ \| ***Varies*** ☐ | | There is Low quality of evidence showing that use of IA r-tPA does not increase the risk of death. There is a Low quality of evidence showing that the use of IV r-tPA was not associated with better functional outcomes compared to no treatment. |
| **Are the undesirable anticipated effects small?** | No ☐ \| Probably No ☐ \| Uncertain ☒ \| Probably Yes ☐ \| Yes ☐ \| ***Varies*** ☐ | | |
| **Are the desirable effects large relative to undesirable effects?** | No ☐ \| Probably No ☐ \| Uncertain ☒ \| Probably Yes ☐ \| Yes ☐ \| ***Varies*** ☐ | ***Summary of the evidence for the relative effect of interventions*:** Please see evidence table and reference list. | See the summary of findings table |

| Outcome | Relative importance | Certainty of the evidence |
|---|---|---|
| *Mortality* | Critical | Very Low |
| *Good functional out-comes** | Critical | Very Low |

**** good functional outcome is defined as modified Rankin score (mRS 0 -2)***

**Reference:**

MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2)(suppl):e1S-e23S.

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | Are the resources required small? | No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐ | No evidence identified | |
| RESOURCE USE | Is the incremental cost small relative to the net benefits? | No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐ | None | |
| EQUITY | What would be the impact on health inequities? | Increased ☐ / Probably increased ☒ / Uncertain ☐ / Probably reduced ☐ / Reduced ☐ / Varies ☐ | None | |
| ACCEPTABILITY | Is the option acceptable to key stakeholders ? | No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐ | None | |
| FEASIBILITY | Is the option feasible to implement? | No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☒ | None | |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
| | ☐ | ☐ | ☒ | ☐ | ☐ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
| | ☐ | ☒ | ☐ | ☐ |

| | |
|---|---|
| **Recommendation (text)** | KSA MOH panel members **suggest not** using combination of IV and IA r-tPA in patients with acute ischemic stroke over IV r-tPA alone. |
| **Justification** | - |
| **Subgroup considerations** | None |
| **Implementation considerations** | - |
| **Monitoring and evaluation** | - |
| **Research priorities** | - |

## Summary of findings table

**Author(s):** Alhazzani W

**Date:** 2013-11-27

### Combination of IV and IA r-tPA compared to IV r-tPA alone for acute ischemic stroke

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk: Risk with IV r-tPA alone | Illustrative comparative risks* (95% CI) Assumed risk: Risk difference with Combination of IV and IA r-tPA | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| **Mortality** | **210 deaths per 1000**[1] | **48 fewer per 1000** (from 107 fewer to 46 more) | **RR 0.77** (0.49 to 1.22)[2] | 343 (2 studies[2]) 90 d | ⨁⊖⊖⊖ **Very Low**[3] due to risk of bias, imprecision |
| **Good functional outcomes, mRS 0-2** | **290 good outcomes per 1000**[2] | **38 more per 1000** (from 35 fewer to 131 more) | **RR 1.13** (0.88 to 1.45)[2] | 343 (2 studies[2]) 90 d | ⨁⊖⊖⊖ **Very Low**[3] due to risk of bias, imprecision |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Baseline mortality rate derived from mortality in control and treatment arms of PROACT I (1998), PROACT II (1999), MELT (2007), and the placebo and control arms of NINDS (1995) as reported in the IMS (2004) study (153 of 727 = 21%). Intervention and control rates were averaged to determine the baseline rate, because the interventions did not have notable effect on mortality.

[2] IMS I (2004) and IMS II (2007). Both studies used the same historical data for their control groups. Historical controls were obtained from the active treatment arm of the NINDS (1995) tPA trial. Control population was limited to patients with baseline NIHSS. 9 and age, 81 y to match the IMS cohorts. We thus combined data from the two studies for the intervention group and compared with the data from the same historical control group. Baseline Good Functional Outcome rate derived from control arms of PROACT I (1998) and PROACT II (1999), MELT (2007) and the placebo control arms of NINDS as reported in the IMS study (99 of 341 5 29%).

[3] CI includes both values indicating harms and benefit.

[4] Major extracranial bleeding not reported as separate outcome because it is captured in the other listed outcomes. Major extracranial bleeding occurred in 2.5% of IV 1 IA-treated patients and 1.1% of IV tPA alone-treated patients (RR, 2.3; 95% CI, 0.4-12.1).

[5] sICH not reported as separate outcome because it is captured in the other listed outcomes. sICH occurred in 13 of 161 patients (8.0%) treated with combined IV 1 IA tPA and in 12 of 182 patients (6.6%) treated with IV tPA alone (RR, 1.23; 95% CI, 0.58-2.57).

**References**

**Observational studies:**

1. Investigators IIT; IMS II Trial Investigators. The Interventional Management of Stroke (IMS) II Study. Stroke. 2007; 38 (7): 2127 - 2135.
2. IMS Study Investigators. Combined intravenous and intraarterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. Stroke. 2004; 35(4): 904 - 911.

Evidence to recommendation framework 6

## Guideline Question: Should mechanical thrombectomy be used in patients with acute ischemic stroke when compared to no thrombectomy?

***Problem:*** Adult patients with acute large vessel anterior circulation ischemic stroke presenting within 8 hours
***Option:*** Thrombectomy
***Comparison:*** medical therapy (no thrombectomy)
***Setting:*** Hospital
***Perspective:*** Individual decision making

***Background:*** Stroke is a common disease that is associated with significant morbidity and mortality. A single center study in KSA showed a prevalence of stroke to be 29 per 100,000 per year; larger and methodologically sound studies are required to accurately describe the prevalence of stroke in KSA. Although the burden of stroke on health care system in KSA appears to be large, there are no data to quantify the impact on patients, policy makers and health care providers.
Reperfusion of ischemic brain tissue may be achieved with the use of thrombolytic therapy. Recombinant tissue plasminogen activator (r-tPA) is used widely to treat patients presenting with acute ischemic stroke, however there is variation in the safety and efficacy of this intervention that depends on multiple factors.

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | Is the problem a priority? | No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐ | See table below | Although no available studies to inform the baseline risk of outcomes in patients with acute ischemic stroke, the risk is probably similar to what is available in literature from other regions in the world. |

| Outcome | Assumed Baseline Risk in Systematic Review | Adult patients with stroke in Saudi Arabia |
|---|---|---|
| Mortality | 210 per 1000 | No epidemiologic studies in the context of Saudi Arabia |
| Good functional outcome | 290 per 1000 | No epidemiologic studies in the context of Saudi Arabia |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| BENEFITS & HARMS OF THE OPTIONS | **What is the overall certainty of this evidence?** | *No included studies* ☐ *Very low* ☐ *Low* ☒ *Moderate* ☐ *High* ☐ | ***The relative importance or values of the main outcomes of interest:*** | There is low quality evidence that did not show clear benefit or harm when using thrombectomy in this context. The results came from asingle RCT (MR RESCUE) that compared mechanical thrombectomy with no thrombectomy in patients with acute ischemic stroke. IV r-tPA was given prior to randomiztion to 43 % and 30% of intervention and control arms, respictvely. This may have attenuated the effect of the intervention. The average time to receivng the intervention was 5.5 hours. Furthermore, The intraarterial administration of t-PA at a dose of as much as 14 mg was allowed as rescue therapy within 6 hours after symptom onset. Subgroup of patints with favourable pneumbral pattern on imaging also did not show any significant benefit from the intervevntion.<br><br>The results of this study failed to show benift of using mechanical thrombectomy over no thrombectomy in patients presenting with acute ischemic stroke within 8 hours. |
| | **Is there important uncertainty about how much people value the main outcomes?** | *Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☒ | **Outcome** / **Relative importance** / **Certainty of the evidence**<br>*Mortality* / Critical / Low<br>*Good functional out-comes** / Critical / Low<br>**** good functional outcome is defined as modified Rankin score (mRS 0 -2)***<br><br>***Summary of the evidence for patients' values and preferences:***<br>Six studies were identified in the systematic review used for the AT9 guidelines, we did not identify any new studies. None of the published studies target KSA population.<br>Individuals who experienced an event, may associate a higher utility to that event compared to those who did not experience the same event.. This factor may be important to consider when eliciting health state valuations for outcomes associated with antithrombotic treatment.<br>Studies also illustrate that other factors such as severity of stroke, sex, age, and living conditions affect the willingness to accept or refuse treatment options.<br>One study suggested that The most significant reason for accepting treatment was the desire to maintain functional independence. | No studies were identified that reflect on values and preferences in the context of Saudi Arabia. Evidence was considered from systematic review used for the AT9 guidelines. |
| | **Are the desirable anticipated effects large?** | *No* ☐ *Probably No* ☒ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | **Reference:**<br>MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: | |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| | Are the undesirable anticipated effects small? | No [X] / Probably No [ ] / Uncertain [ ] / Probably Yes [ ] / Yes [ ] / Varies [ ] | American College of Chest Physicians evidence<br><br>***Summary of the evidence for the relative effect of interventions***:<br>Please see evidence table and reference list. | |
| | Are the desirable effects large relative to undesirable effects? | No [ ] / Probably No [ ] / Uncertain [X] / Probably Yes [ ] / Yes [ ] / Varies [ ] | | See the summary of findings table |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | Are the resources required small? | No [X] / Probably No [ ] / Uncertain [ ] / Probably Yes [ ] / Yes [ ] / Varies [ ] | No evidence identified | |
| RESOURCE USE | Is the incremental cost small relative to the net benefits? | No [ ] / Probably No [X] / Uncertain [ ] / Probably Yes [ ] / Yes [ ] / Varies [ ] | None | |
| EQUITY | What would be the impact on health inequities? | Increased [ ] / Probably increased [X] / Uncertain [ ] / Probably reduced [ ] / Reduced [ ] / Varies [ ] | None | |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|
| ACCEPTABILITY | **Is the option acceptable to key stakeholders ?** | *No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | None | The intervention may be acceptable for patients, some physicians. However, may not be that appealing for policymakers issues of cost, and the need for health professionals training. |
| FEASIBILITY | **Is the option feasible to implement?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☒ | None | The feasibility is variable depending on the center and geographic location. |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☐ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☒ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☐ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option ☐ | We suggest not offering this option ☒ | We suggest offering this option ☐ | We recommend offering this option ☐ |

| | |
|---|---|
| **Recommendation (text)** | KSA MOH panel members **suggest not** using mechanical thrombectomy in the management of patients with acute ischemic stroke. |
| **Justification** | - |
| **Subgroup considerations** | None |
| **Implementation considerations** | None |
| **Monitoring and evaluation** | None |
| **Research priorities** | Future guidelines should address questions comparing mechanical thrombectomy to standard of care IV r-tPA in patients with acute ischemic stroke |

## Summary of findings table

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**Date:** 2013-11-27

### Mechanical Thrombectomy compared to No Mechanical Thrombectomy for acute ischemic stroke

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk | | Relative effect (95% CI) | No of Participants (studies) Follow-up | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | **Risk with medical therapy** | **Risk difference with Thrombectomy** | | | |
| **Mortality** | **210 deaths per 1000** | **53 fewer deaths per 1000** (from 153 fewer to 117 more) | **OR 0.73** (0.30 to 1.76)[4] | 118 (1 study[1]) 90 days | ⨁⨁◯◯ **LOW**[2,3] due to indirectness, imprecision |
| **Good functional outcome, mRS 0-2** | **290 good outcomes per 1000** | **16 fewer good outcomes per 1000** (from 117 fewer to 160 more) | **OR 0.90** (0.36 to 2.25)[4,5] | 118 (1 study[1]) 90 days | ⨁⨁◯◯ **LOW**[2,3] due to indirectness, imprecision |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Kidwell et al. (MR RESCUE); other studies were not included due to use of different control group (IMS III), or lack of subgroup data (SYNTHESIS Expansion).
[2] IV r-tPA was used in both groups prior to randomization, 28 of 64 (43%) in the thrombectomy group, and 16 of 54 (29.6%) in the standard medical therapy group. Hence we lowered for indirectness.
[3] Wide CI that included significant harm and significant benefit
[4] Data from Kidwell et al.
[5] Symptomatic ICH developed in 3 patients out of 64 (4.7%) in the thrombectomy group and 2 out of 52 patients in the control group (OR1.22; 95% CI 0.21 to 7.02)

**References**

**Randomized trials:**

1. Kidwell CS, Jahan R, Gornbein J, Alger JR. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med. 2013 Mar 7;368(10):914-23.


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