**SUPPLEMENTAL MATERIAL**

**EFFICACY AND SAFETY OF THROMBOLYTIC THERAPY FOR** **STROKE WITH UNKNOWN TIME OF ONSET: A META-ANALYSIS**

**Supplemental Methods**

**Electronic search strategy:**

**I. Pubmed**

1. “streptokinase”[Text Word] OR “urokinase”[Text Word] OR “tissue plasminogen activator”[Text Word] OR “t-PA”[Text Word] OR “recombinant tissue plasminogen activator”[Text Word] OR “rt-PA”[Text Word] OR “alteplase”[Text Word] OR “activase”[Text Word] OR “reteplase”[Text Word] OR “retavase”[Text Word] OR “tenecteplase”[Text Word] OR “tnkase”[Text Word] OR “desmoteplase”[Text Word] OR “lanoteplase”[Text Word] OR “monteplase”[Text Word] OR “thrombolysis”[Text Word] OR “thrombolyzed”[Text Word] OR “recanalization”[Text Word]
2. “administration, intravenous”[Mesh] OR “infusions, intra-arterial”[Mesh] OR “reperfusion”[Mesh] OR “cerebral revascularization”[Mesh]
3. “brain ischemia”[Mesh] OR “stroke”[Mesh] OR “acute stroke”[Text Word] OR “acute ischaemic stroke”[Text Word] OR “stroke with unknown time of onset”[Text Word] OR “unknown onset stroke”[Text Word] OR “unclear-onset stroke”[Text Word] OR “wake up stroke”[Text Word] OR “stroke on awakening”[Text Word]
4. AND/1-3
5. (randomized[tiab] OR placebo[tiab] OR controlled[tiab] OR random\*[tiab] OR “rct”[text word] OR trial\*[tiab] OR groups[tiab]) AND (mask\*[tiab] OR blind\*[tiab])
6. retrospective[tiab] OR prospective [tiab] OR (cross[tiab] AND sectional[tiab]) OR longitudinal[tiab] OR (case[tiab] AND control[tiab]) OR case-control[tiab] OR cohort\*[tiab] OR observational[tiab] OR population based[tiab]
7. OR/5-6
8. 4 AND 7

**II. Embase**

1. (streptokinase OR urokinase OR “tissue plasminogen activator” OR t-PA OR “recombinant tissue plasminogen activator” OR rt-PA OR alteplase OR activase OR reteplase OR retavase OR tenecteplase OR tnkase OR desmoteplase OR lanoteplase OR monteplase OR thrombolysis OR thrombolyzed OR recanalization):ti,ab
2. ‘intravenous drug administration’/exp OR ‘intraarterial drug administration’/exp OR ‘cerebral revascularization’/exp
3. ‘stroke’/exp OR ‘brain ischemia’/exp OR ‘acute stroke’/exp OR ‘acute ischaemic stroke’/exp OR ‘stroke with unknown time of onset’/exp OR ‘unknown onset stroke’/exp OR ‘unclear-onset stroke’/exp OR ‘wake up stroke’/exp OR ‘stroke on awakening’/exp
4. AND/1-3
5. ((random\* OR control\* OR trial\* OR placebo):ti,ab OR ‘rct’:ti,ab) AND (mask\* OR blind\*):ti,ab
6. (retrospective OR (cross near/1 sectional) OR longitudinal OR (case near/1 control) OR cohort\* OR observational OR (population near/1 based)):ti,ab
7. OR/5-6
8. 4 AND 7

**III.** **Cochrane Library**

1. MESH descriptor “Tissue Plasminogen Activator” explodes all trees
2. (“streptokinase” OR “urokinase” OR “tissue plasminogen activator” OR “t-PA” OR “recombinant tissue plasminogen activator” OR “rt-PA” OR “alteplase” OR “activase” OR “reteplase” OR “retavase” OR “tenecteplase” OR “tnkase” OR “desmoteplase” OR “lanoteplase” OR “monteplase” OR “thrombolysis” OR “thrombolyzed” OR “recanalization”):title, abstract, keywords
3. OR/1-2
4. MeSH descriptor “Brain Infarction” explodes all trees
5. MeSH descriptor "Stroke, Acute" explodes all trees
6. (“brain ischemia” OR “stroke” OR “acute stroke” OR “acute ischaemic stroke” OR “stroke with unknown time of onset” OR “unknown onset stroke” OR “unclear-onset stroke” OR “wake up stroke” OR “stroke on awakening”):title, abstract, keywords
7. OR/4-6
8. MESH descriptor "Administration, Intravenous" explode all trees
9. MESH descriptor "Infusions, Intra-Arterial" explode all trees
10. OR/9-10
11. 3 AND 7 AND 10

**Supplemental Tables and Figures**

**Table I. Characteristics extracted from included studies.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Study Design** | **Patients\*** | **Age (yrs)** | **Gender (male, %)** | **Stroke/TIA, n (%)** | **AF, n (%)** | **CHD, n (%)** | **HPT, n (%)** | **DM, n (%)** | **Smoking, n (%)** | **Dyslipidemia, n (%)** | **NIHSS score** |
| **Thrombolyzed UTOS patients vs. non-thrombolyzed UTOS patients**  |
| Barreto, 2009 | Retro | 46/34 | 62 (14) /64 (13) | 11 (39) /15 (44) | NR | NR | 8 (17)/5 (15) | 18 (65) /22 (65) | 6 (21) /11 (33) | NR | 12 (27)/9 (27) | 16 (3-24) /10.5 (2-26) |
| Roveri, 2013 | Pro | 9/51 | 59.22 (13.13) /70.43 (10.28) | 33 (55) /48 (55.8) | 14 (23.3)/21 (24.4) | NR | 24 (40) /45 (52.3) | 36 (60) /55 (64) | 14 (23.3)/10 (11.6) | 12 (20.7)/21 (25.9) | 19 (31.7)/30 (34.9) | 9 (4-19)/7 (4-18) |
| Kim, 2011 | Retro | 29/49 | 66.89 (12.37) /71.67 (9.04) | 17 (58.6)/29 (59.2) | 2 (6.9) /20 (40.8) | 5 (17.2) /19 (38.8) | NR | 15 (51.7)/29 (59.2) | 8 (27.6) /11 (22.4) | 13 (44.8)/23 (46.9) | 10 (34.5) /9 (18.4) | 13/12 |
| Anaissie, 2016 | Pro | 46/154 | 69/63 | 22 (47.9)/85 (55.2) | NR | 6 (13) /21 (13.6) | NR | 36 (78.3)/119 (77.3) | 20 (43.5)/45 (29.2) | NR | 19 (41.3)/60 (39) | 9.5 (1-27)/5 (0-33) |
| Breuer, 2010 | Retro | 10/35 | 73/66 | 5 (50)/23 (66) | 5 (50)/9 (26) | 3 (30)/6 (17) | 3 (30)/6 (17) | 9 (90) /29 (83) | 4 (40)/13 (37) | NR | 8 (80)/27(77) | 10.5 (1-22)/6 (1-21) |
| Manawadu, 2013 | Pro | 68/54 | NR | 23 (33.8)/28 (51.9) | NR | 21 (30.9) /9 (16.7) | NR | 45 (66.2)/32 (59.3) | 14 (20.6)/13 (24.1) | NR | NR | 11 (8-17)/9.5 (5-16) |
| Thomalla, 2018 | Pro | 254/249 | 65.3 (11.2)/65.2 (11.9) | 165 (65.0)/160 (64.3) | 37 (14.6) /31 (12.4) | 30 (11.8)/ 29 (11.6) | NR | 135 (53.1) /131 (52.6) | 43 (16.9) /39 (15.7) | NR | 93 (36.6) /85 (34.1) | 6 (4–9) /6 (4–9) |
| **Thrombolyzed UTOS patients vs. thrombolyzed KOS patients**  |
| Barreto, 2009 | Retro | 28/174 | 62 (14)/65 (15) | 18 (39)/97 (56) | NR | NR | 8 (17)/38 (22) | 30 (65) /125 (72) | 10 (20)/48 (28) | NR | 12 (27)/35 (22) | 16 (3-24) /11 (1-35) |
| Cho, 2008 | Retro | 32/223 | 67.1 (11.0)/65.8 (12.5) | 17 (53.1)/128 (57.4) | NR | NR | NR | 22 (68.8)/133 (59.6) | 8 (25.0)/61 (27.4) | 8 (25)/66 (29.6) | 9 (28.1)/55 (24.7) | 14.5 (5-30) /13 (2-32) |
| Morelli, 2015 | Pro | 27/143 | 72.2/71.3 | 13 (52.1)/72 (49.7) | 4 (13.1)/20 (14) | 10 (36.6) 121 (18.7) | NR | 19 (69.4) /87 (61.2) | 6 (21.7) /40 (28.1) | 3 (12.5) /26 (18.6) | 8 (28.2) /43 (30.3) | 11.9/11.4 |
| Roveri, 2013 | Pro  | 60/86 | 68.75 (11.37) /65.64 (12.42) | 33 (55.0) /48 (55.8) | 14 (23.3) /21 (24.4) | NR | 24 (40) /45 (52.3) | 36 (60)/55 (64) | 14 (23.3) /10 (11.6) | 12 (20.7) /21 (25.9) | 19 (31.7) /30 (34.9) | 7.5 (4-18.5) /11.0 (7-17) |
| Anaissie, 2016 | Pro | 46/369 | 69/64 | 22 (52.2) /187 (49.3) | NR | 6 (13)/44 (12) | NR | 36 (78.3) /283 (76.6) | 20 (43.5) /107 (29) | NR | NR | 9.5 (1-27) /8 (0-39) |
| Aoki, 2013 | Pro | 20/60 | 83/82 | 8 (40)/30 (50) | 0 (0) /8 (13) | 14 (70)/36 (60) | 3 (15) /5 (8) | 18 (90)/46 (77) | 6 (30)/15 (25) | 6 (30)/21 (35) | 7 (35) /8 (30) | 18 (13-20) /17 (12-20) |
| Bai, 2013 | Pro | 48/138 | 61.2 (13) /59.4 (9.8) | 32 (66.67) /95 (68.84) | NR | 5 (10.42) /17 (12.32) | NR | 36 (75) /106 (76.81) | 6 (12.5) /16 (11.59) | NR | NR | 10.92 (4.08) /10.86 (4.95) |
| Ebinger, 2012 | Pro | 17/131 | 81/75 | 7 (41.2) /57 (43.5) | 4 (23.5) /36 (27.5) | 9 (52.9) /46 (35.1) | 2 (11.8) /19 (14.5) | 14 (82.4) /109 (83.2) | 4 (23.5) /31 (23.7) | 4 (23.5) /24 (18.3) | 8 (47.1) /58 (44.6) | 13 (8-16) /8 (5-16) |
| Manawadu, 2013 | Pro | 68/326 | 73.9 (15.6)/72.8 (14.7) | 23 (34)/155 (48) | NR | 21 (31)/79 (24) | 23 (34)/90 (28) | 45 (66) /185 (57) | 14 (21)/54 (17) | 8 (12)/43 (13) | 22 (32)/95 (29) | 13 (7-15) /12 (8-17) |

\*No. of patients in the form of treatment/control; UTOS, stroke with unknown time of onset; KOS, known-onset stroke**;** TIA, transient ischemic attack; AF, atrial fibrillation; CHD, coronary heart disease; HPT, hypertension; DM, diabetes mellitus; NIHSS, NIH Stroke Scale; NR, not reported; Pro, prospective trial; Retro, retrospective study.

**Table II. The evaluation of bias in accordance with Hayden’s criteria.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Study Participation** | **Study Attrition** | **Prognostic Factor Measurement** | **Outcome Measurement** | **Confounding Measurement and Account** | **Analysis** | **Total Score** |
| Anaissie, 2016 | High  | Moderate | Moderate | Low | Moderate | Low  | 10 |
| Aoki, 2013 | Moderate | Low | Moderate | Moderate | Moderate | Low | 9 |
| Bai, 2013 | Moderate | Low | Low | Low | Low | Moderate | 10 |
| Barreto, 2009 | Moderate | Low | Moderate | High  | Low | Moderate | 9 |
| Breuer, 2010 | Low | Moderate | Low | Low | Moderate | High | 8 |
| Cho, 2008 | Moderate | Unsure | Moderate | Low | Unsure | Low | 7 |
| Ebinger, 2012 | Low  | Low  | Moderate | Unsure | Moderate | Moderate | 11 |
| Kim, 2011 | Moderate | Moderate | Low | Low | Moderate | Unsure | 9 |
| Manawadu, 2013 | Moderate | Low | Moderate | Moderate | High | Moderate | 8 |
| Morelli, 2015 | Moderate | Moderate | Low | Low | Moderate | Low | 7 |
| Roveri, 2013 | High  | Low  | Moderate | Moderate | Low | Low | 9 |
| Thomalla, 2018 | Low | Low  | Low | Low | Low | Low | 6 |

Low, low risk of bias; Moderate, moderate risk of bias; High, high risk of bias.



**Figure I.** Funnel plot of clinical outcomes based on mRS scores of 0-2 among studies (with pseudo 95% confidence). **A,** Functional outcomes comparing thrombolyzed UTOS patients vs. non-thrombolyzed UTOS patients. **B,** Functional outcomes comparing thrombolyzed UTOS patients vs. thrombolyzed KOS patients.



**Figure II.** Funnel plot of the safety of thrombolysis among studies (with pseudo 95% confidence). **A** and **B**, Incidence of SICH at 90 days comparing thrombolyzed UTOS patients vs. non-thrombolyzed UTOS patients (A) and thrombolyzed UTOS patients vs. thrombolyzed KOS patients (B). **C** and **D**, Mortality within 90 days comparing thrombolyzed UTOS patients vs. non-thrombolyzed UTOS patients (C) and thrombolyzed UTOS patients vs. thrombolyzed KOS patients (D).