**APPENDICES**

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# Appendices

## Appendix 1: Literature Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2015>, EBM Reviews - Health Technology Assessment <1st Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2015>, Embase <1980 to 2015 Week 10>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp Brain Ischemia/ (198337)

2 ((isch?emi\* adj3 (stroke\* or apoplex\* or cerebr\* or brain or encephalopath\* or neur\*)) or AIS).tw. (198076)

3 exp Stroke/ (189703)

4 (stroke\* adj3 (acute or cerebr\* or attack\* or accident\* or lacunar or cardioembol\*)).tw. (76907)

5 Intracranial Arteriosclerosis/ (10347)

6 exp "Intracranial Embolism and Thrombosis"/ (367169)

7 Carotid Artery Thrombosis/ (5356)

8 ((occlus\* or block\* or infarct\* or clot\* or termination) adj6 (carotid or cerebr\* or MCA or ACA)).tw. (96218)

9 or/1-8 (786703)

10 exp Thrombectomy/ (15008)

11 Embolectomy/ (4255)

12 ((Mechanical adj3 (thromb\* or embol\* or clot disruption\* or clot retrieval\*)) or ((clot\* or thromb\* or embol\*) adj3 (retriev\* or disruption\* or fragmentation)) or ((stent\* or stent-assisted) adj3 retriev\*) or stentriever\*).tw. (9056)

13 ((Merci or Trevo or Penumbra or Solitaire) adj3 (retriever\* or system\* or device\*)).mp. (1233)

14 or/10-13 (24914)

15 9 and 14 (14515)

16 exp Animals/ not (exp Animals/ and Humans/) (8045601)

17 15 not 16 (14213)

18 (case reports or congresses).pt. (1780093)

19 17 not 18 (13866)

20 limit 19 to english language [Limit not valid in CDSR,DARE; records were retained] (12321)

21 limit 20 to yr="2005 -Current" [Limit not valid in DARE; records were retained] (9737)

22 21 use pmoz,cctr,coch,dare,clhta,cleed (970)

23 exp Brain Ischemia/ (198337)

24 ((isch?emi\* adj3 (stroke\* or apoplex\* or cerebr\* or brain or encephalopath\* or neur\*)) or AIS).tw. (198076)

25 exp Cerebrovascular Accident/ (189703)

26 Stroke Patient/ (13478)

27 (stroke\* adj3 (acute or cerebr\* or attack\* or accident\* or lacunar or cardioembolic)).tw. (76838)

28 exp Occlusive Cerebrovascular Disease/ (26483)

29 exp Carotid Artery Obstruction/ (25862)

30 Brain Embolism/ (8515)

31 ((occlus\* or block\* or infarct\* or clot\* or termination) adj6 (carotid or cerebr\* or MCA or ACA)).tw. (96218)

32 or/23-31 (478286)

33 Mechanical Thrombectomy/ (1828)

34 Thrombectomy/ (10732)

35 Embolectomy/ (4255)

36 ((Mechanical adj3 (thromb\* or embol\* or clot disruption\* or clot retrieval\*)) or ((clot\* or thromb\* or embol\*) adj3 (retriev\* or disruption\* or fragmentation)) or ((stent\* or stent-assisted) adj3 retriev\*) or stentriever\*).tw. (9056)

37 ((Merci or Trevo or Penumbra or Solitaire) adj3 (retriever\* or system\* or device\*)).mp. (1233)

38 or/33-37 (22583)

39 32 and 38 (4742)

40 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38090949)

41 exp humans/ or exp human experimentation/ or exp human experiment/ (29700691)

42 40 not 41 (8416467)

43 39 not 42 (4642)

44 case report/ or conference abstract.pt. (5381946)

45 43 not 44 (2728)

46 limit 45 to english language [Limit not valid in CDSR,DARE; records were retained] (2466)

47 limit 46 to yr="2005 -Current" [Limit not valid in DARE; records were retained] (2248)

48 47 use emez (1362)

49 22 or 48 (2332)

50 remove duplicates from 49 (1624)

## Appendix 2: Evidence Quality Assessment

Table A1: GRADE Evidence Profile for Comparison of Mechanical Thrombectomy and Best Medical Therapy on Clinical Outcomes

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Number of Studies (Design)** | **Risk of Bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication Bias** | **Upgrade Considerations** | **Quality** |
| **Functional Independence (mRS)** |
| 5 (RCTs) | No serious limitations | No serious limitations | No serious limitations | No serious limitationsa | Undetected | No other considerations | ⊕⊕⊕⊕ High |
| **Mortality** |  |  |  |  |  |  |  |
| 5 (RCTs) | No serious limitations | No serious limitations | No serious limitations  | Serious limitations (–1)a | Undetected | No other considerations | ⊕⊕⊕ Moderate |
| **SICH** |  |  |  |  |  |  |  |
| 5 (RCTs) | No serious limitations | No serious limitations | No serious limitations | Serious limitations (–1)a | Undetected | No other considerations | ⊕⊕⊕ Moderate |
| **Reperfusion** |  |  |  |  |  |  |  |
| 5 (RCTs) | No serious limitations | No serious limitations | No serious limitationsb | Serious limitations (–1)a | Undetected | No other considerations | ⊕⊕⊕ Moderate |
| **Recanalization** |  |  |  |  |  |  |  |
| 3 (RCTs) | No serious limitations | No serious limitations | Serious limitations (–1)c | Serious limitations (–1)a | Undetected | No other considerations | ⊕⊕ Low |

Abbreviations: mRS, modified rankin scale; SICH, symptomatic intracranial hemorrhage

aOptimal information size (OIS) may not be met for this outcome as 4 out of 5 RCTs were stopped early.

bReperfusion can be considered a surrogate outcome.

cRecanalization can be considered a surrogate outcome.

Table A2: Risk of Bias Among Randomized Controlled Trials for the Comparison of Mechanical Thrombectomy and Clinical Outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author, Year** | **Allocation Concealmenta** | **Blindingb** | **Complete Accounting of Patients and Outcome Events** | **Selective Reporting Bias** | **Other Limitations** |
| Berkhemer et al, 2014 | No limitations | No limitations | No limitations | Limitationsc | No limitationsf |
| Campbell et al, 2015 | No limitations | No limitations | No limitations | No limitations | Limitationse,f |
| Goyal et al, 2015 | No limitations | No limitations | No limitations | Limitationsd | Limitationse,f |
| Jovin et al, 2015 | No limitations | No limitations | No limitations | No limitations | Limitationse,f |
| Saver et al, 2015 | No limitations | No limitations | No limitations | No limitations | Limitationse,f |

Abbreviations:

aAll 5 RCTs used a web-based randomized minimization procedure.

bAll 5 included RCTs had blind outcome evaluation but physicians conducting the intervention were aware of treatment assignment. This was appropriate as a sham procedure was not ethical and standard of care is intravenous thrombolysis which is a more appropriate comparator.

cRCT protocol states the functional outcome measured by ‘Academic Linear Disability Scale’ would be collected at 90 days, but this outcome is not reported in the published article.

dRCT protocol states the functional outcome measured by ‘miFUNCTION scale’ would be collected, but this outcome is not reported in the published article.

eAfter the Berkhemer et al (2015) study was presented at the World Stroke Conference in October 2014, the 4 following RCTs stopped early based on prespecified boundary for efficacy during interim analysis.

fAll studies had grant support from Covidien/ev3 (the company that manufactures the Solitaire FR stent retriever) and/or other manufacturers/industry support.

## Appendix 3: Subgroup Results



Figure A1: Risk Difference of Mechanical Thrombectomy Versus Best Medical Therapy on Proportion of Functionally Independent Patients at 90-Day Follow-up



Figure A2: Mechanical Thrombectomy Versus Best Medical Therapy on the Proportion of Functionally Independent Patients at 90-Day Follow-up by Status of IVT



**\***Goyal et al divided age in <=80 years and >80 years in the age sensitivity analysis.

Figure A3: Mechanical Thrombectomy Versus Best Medical Therapy on the Proportion of Functionally Independent Patients at 90-Day Follow-up by Age, Secondary Analysis

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Figure A4: Mechanical Thrombectomy Versus Best Medical Therapy on the Proportion of Functionally Independent Patients at 90-Day Follow-up by Occlusion Site



\*Goyal et al estimate not included in this sensitivity analysis as this trial divided patients into <=80 years and >80 years and we wanted to determine if the estimate influenced results.

Figure A5: Mechanical Thrombectomy Versus Best Medical Therapy on Proportion of Functionally Independent Patients at 90-Day Follow-up by Age, Secondary Analysis without ESCAPE Study

## Appendix 4: Secondary Outcome Results

Table 1: Reperfusion and Recanalization Rates in Included RCTs

| **Author, Year** | **Intervention** | **Control** | **Adjusted Value (95% CI)** |
| --- | --- | --- | --- |
| **Berkhemer et al** |  |  |  |
| Reperfusion | 115/196 (58.7%)a | NR | NR |
| Recanalization | 141/187 (75.4%)b | 68/207 (32.9%)b | 6.88 (4.34 to 10.94) |
| **Campbell et al** |  |  |  |
| Reperfusion | 100 (100 to 100)c | 37 (-0.5 to 96) | 4.7 (2.5 to 9.0)d |
| Recanalization | 33 (94%)e | 15 (43%)e | 29.0 (5.4 to 155.0)d |
| **Goyal et al**  |  |  |  |
| Reperfusion | 113/156 (72.4%)f:79/112 (70.5%) with IVT34/44 (77%) w/o IVT | NR | NR |
| Recanalization | NR | 43/138 (31.2%)g:41/110 (32.3%) with IVT2/28 (7%) w/o IVT | NR |
| **Jovin et al**  |  |  |  |
| Reperfusion | 67/102 (65.7%)a | NR | NR |
| Recanalization | NR | NR | NR |
| **Saver et al** |  |  |  |
| Reperfusion | 73/83 (88%)a 53/64 (83%)h | 21/52 (40%) | 2.05 (1.45 to 2.91)d |
| Recanalization | NR | NR | NR |

Abbreviations: IVT, intravenous thrombolysis, NR, not reported

aReperfusion was measured by the modified Thrombolysis in Cerebral Infarction (TICI) score where a score of 2b or 3, indicating complete filling of the expected vascular territory – no./total no. (%).

bMeasured as number of patients with no intracranial occlusion on follow-up CT angiography – no./total no. (%).Data for follow-up CT angiography were not available for 106 patients owing to imminent death or death (24 patients), decreased kidney function (13 patients), insufficient scan quality (5 patients), and other reasons (64 patients).

cReperfusion was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and 24-hour imaging (IQR). This value can be negative if hypoperfusion becomes more severe over time. This analysis was adjusted for the site of vessel occlusion at baseline.

dP<0.001.

eRecanalization was defined as a Thrombolysis in Myocardial Infarction score of 2 or 3 (partial or complete restoration of flow at the site of arterial occlusion) and measured at 24 hours. This analysis was adjusted for the site of vessel occlusion at baseline.

fReperfusion was measured by the Thrombolysis in Cerebral Infarction (TICI) score where a score of 2b or 3, indicating complete filling of the expected vascular territory – no./total no. (%).

gRecanalization was measured by a modified Arterial Occlusive Lesion (AOL) score of 2 or 3 indicates partial or complete recanalization – no./total no.

hSaver et al also reported successful reperfusion at 27 hr. – no./total no (%). Successful reperfusion was defined as reperfusion at least 90%, as assessed with the use of perfusion CT or MRI. Data on successful reperfusion were not obtained for all patients after the adoption of the protocol amendment making penumbral imaging optional