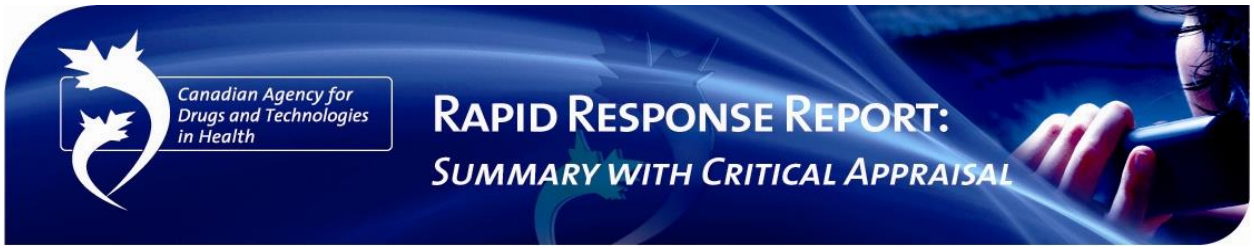

TITLE: Endovascular Therapy for Patients with Ischemic Stroke: A Review of the Clinical and Cost-Effectiveness and Guidelines

DATE: 14 August 2015; REVISED 6 October 2015

CONTEXT AND POLICY ISSUES

Acute ischemic stroke (AIS) occurs when a cerebral artery becomes occluded with a blood clot or other thrombi. The occlusion prevents oxygen from flowing to the brain, thereby causing brain tissue death and focal neurological deficits from temporary or permanent infarction.[1] Treatment constitutes recanalization (i.e. relieving the occlusion) and reperfusion (restoring blood flow) of ischemic cranial penumbra (i.e. hypoperfused brain tissue at-risk of permanent infarction). AIS is associated with high mortality rates particularly in patients in whom treatment is delayed. The incidence of AIS is estimated at 40,000 a year in Canada.[2]

The established first-line method for treating AIS is intravenous (IV) thrombolysis which involves inducing reperfusion with tissue plasminogen activator (tPA) or other thrombolytic medications within the first 4.5 hours of stroke onset (three hours for high-risk patients).[3] For patients contraindicated to IV thrombolysis, those with large artery occlusions, or those that present outside the ideal treatment time window for IV thrombolysis, alternate forms of therapy must be explored.

Endovascular therapy (EVT) represents one such alternate option to facilitate recanalization or reperfusion of occluded vessels. The term EVT encompasses multiple procedures. EVT includes thrombectomy, the mechanical disintegration of vessel-occluding thrombi or blood clots, with or without intra-arterial (IA) administration of thrombolytic medications.[1,3] For thrombectomy, specialized devices and thrombolytic medications are delivered to occluded sites with the aid of microcatheters and guidewires. The devices, including aspiration devices, coils, stents, and retrievers, disintegrate and remove thrombi or blood clots from the affected area.

EVT is associated with risks such as mechanical damage to the arterial wall, fragmentation and distal embolization of the thrombus, and systemic and cerebral hemorrhage.[4] Prior to administering EVT, it is necessary to carefully identify and select patients who are contraindicated for IV thrombolysis or for whom the benefits of EVT outweigh the risks.

Diagnostic imaging technologies such as magnetic resonance imaging (MRI) or computed tomography (CT) may be used to identify those patients who are contraindicated to IV tPA or who will, for other reasons, benefit more from EVT than from IV tPA. Imaging helps to determine occlusion characteristics, such as vessel location, type, and size of occlusions, and to identify salvageable ischemic tissue.[5]

The purpose of this review, therefore, is to examine the available evidence and evidence-based guidelines on the clinical effectiveness and cost-effectiveness of EVT relative to IV tPA for patients suffering from AIS. In addition, a review of the costs associated with diagnostic imaging for selecting patients for EVT is included.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and clinical benefit of endovascular therapy for patients who have undergone ischemic stroke?

2. What is the cost-effectiveness of endovascular therapy for patients who have undergone ischemic stroke?

3. What are the costs and equipment requirements associated with the diagnostics before and during endovascular therapy, specifically regarding computed tomography angiography and magnetic resonance angiography?

4. What are the evidence-based guidelines associated with endovascular therapy for patients who have undergone ischemic stroke?

KEY FINDINGS

Three MAs and one SR suggested that the incidence of favourable outcomes was higher in patients treated with EVT compared with patients treated with a comparator, and four MAs reported no statistically significant difference. Six MAs reported no statistically significant differences in rates of symptomatic intracerebral/intracranial hemorrhage (sICH), whereas one SR reported a higher rate with patients treated with EVT compared with the alternative treatment. The seventh MA did not report on sICH. There was no statistically significant difference in mortality reported in five MAs and one SR, lower mortality in one MA, and higher mortality in one MA for patients treated with EVT compared with patients who underwent an alternative therapy. Limited evidence from economic studies suggests that EVT is cost-effective relative to IV tPA under specific conditions. The evidence-based guidelines recommend the use of EVT, primarily in patients who are contraindicated to IV thrombolysis.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), economic

studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and July 16, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients who have undergone ischemic stroke (e.g.; have major artery block with clot present) whose clots have been visualized using either computed tomography angiography (CTA) or magnetic resonance angiography (MRA)
Intervention	Endovascular therapy (EVT) (e.g. a stent retrieval system used for thrombectomy [e.g. Merci Retrieval system])
Comparator	Patients treated with tissue plasminogen activator (tPA); Patients not eligible for tPA treatment; Standard treatment (includes stabilization and the provision of rehabilitation services)
Outcomes	Q1: Clinical effectiveness and clinical benefit (e.g. but not limited to, post-stroke functional outcomes/levels of independence (most important) and mortality, safety, harms and risks); Q2: Cost-effectiveness of endovascular therapy; Q3: Cost and technical/equipment requirements associated with the diagnostics before and during endovascular therapy procedure (includes CTA and MRA); Q4: Evidence-based guidelines
Study Designs	Systematic reviews, meta-analyses, randomized controlled trials, economic studies, and guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Primary studies included in SRs or MAs were excluded. Non-comparative studies and those comparing two forms of EVT were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the Assessment of Multiple Systematic Reviews (AMSTAR) tool,[6] economic studies were assessed using the Drummond checklist,[7] and guidelines were assessed with the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument.[8] Summary scores were not calculated for the included

studies; rather, a review of the strengths and limitations of each included study were described. A formal critical appraisal of cost studies was not conducted. Limitations of these studies will be included in the limitations section.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 553 citations were identified in the literature search. Following screening of titles and abstracts, 491 citations were excluded and 62 potentially relevant reports from the electronic search were retrieved for full-text review. One additional study was retrieved from the grey literature. Twenty-two publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

A detailed description of individual study characteristics is provided in Tables A1 to A4 of APPENDIX 2: Characteristics of Included Publications.

Study Design

The evidence included was derived from seven MAs[3,9-14], two SRs,[1,15] five economic evaluations,[5,16-19] five cost summary studies,[20-24] and three evidence-based guidelines.[25-27] Of the nine SRs and MAs, five were published in 2015 and the remaining were published prior to 2015. The SRs and MAs analyzed data from overlapping sets of primary studies published between 1990 and 2015. Two MAs pooled data from primary studies published between 2013 and 2015.[9,12] The remaining SRs and MAs included primary studies published between 1999 and 2015. One SR reported data from primary studies without pooling.[1]

Country of Origin

One MA each was based in China,[11] and Sweden,[9] and four were based in the United States.[3,10,12,14] One was done by collaborators in the United States and Peru.[13] Both SRs came from authors in the United States.[1,15]

Four economic studies[5,17-19] were conducted by authors based in the United States and one was done in the Netherlands.[16] Four of the cost summary studies[21-24] were done in the United States and the fifth was done in France.[20]

Two evidence-based guidelines were written in the United States[25,27] and one in Canada.[26]

Patient Population

All SRs and MAs included adult patients who had AIS following vessel occlusions. The economic studies[5,16-19] involved hypothetical patients with AIS. One cost-utility analysis was based on a cohort of patients presenting within 3 hours of stroke symptoms and with intraluminal thrombuses that could be treated with intra-arterial procedures.[5] Patient ages ranged from 50 to 90 years. The study was done from the perspective of the payer. The second cost-utility analysis, taken from the perspective of society, involved a cohort of 65 year old patients with occlusion of a major intracranial artery presenting more than 3 hours after onset of

stroke.[19] The third cost-utility analysis, also written from the perspective of society, involved a single 65 year old patient with large vessel occlusion/[18] The fourth cost-utility analysis did not report its perspective and was based on a cohort of 65 year old patients with unspecified occlusion location.[17] The single cost-effectiveness analysis written from the perspective of the patient, involved patients eligible for EVT.[16]

Interventions and Comparators

Interventions primarily involved the use of EVT devices for mechanical thrombectomy (i.e. disruption and removal of blood clots) with or without IA or IV thrombolysis. All studies included a mechanical component in the intervention. The comparator was IV thrombolysis.[1,3,9-15] Thrombolysis was performed with medications such as rtPA (alteplase), heparin or urokinase. Cost summary studies that involved EVT without comparators were included.

The most commonly studied EVT devices were the MERCI retriever, the Penumbra System, the TREVO stent retriever, and the Solitaire Neurovascular Remodeling Device or stent retriever.

Outcomes

Efficacy outcomes were measured 90 days following treatment. The functional outcome of patients measured by the modified Rankin Scale score (mRS) specifies whether a patient has no symptoms (0), has clinically significant disabilities (1), has slight disability (2), has moderate disability (3), has moderately severe disability (4), has severe disability or is bedridden (5), or dies (6).[4] A patient is classified as having functional independence or favourable outcome if their mRS ≤ 2. The most commonly reported outcomes were the proportion of patients who achieved favourable outcome (mRS),[1,3,9-15] the proportion of patients who had symptomatic intracerebral/intracranial hemorrhage (sICH),[1,3,9,11-15] or the proportion of patients who died.[1,3,9-15]

Summary of Critical Appraisal

A detailed description of individual study characteristics is provided in Tables A5 to A8 of APPENDIX 3: Critical Appraisal of Included Publications.

The quality of evidence retrieved was moderate. Authors of one SR[1] and six MAs[9-14] limited the design of included studies to RCTs. Authors of one MA[3] and one SR[15] did not specify study type in their inclusion criteria. All SRs were based on literature searches, but it was unclear whether the searches were comprehensive in all of the reviews. Publication bias was apparent as the literature search timeframe ranged from three to five years for some reviews.[9,12,14] One SR[15] and one MA[13] provided a list of excluded studies.

One of the five cost-effectiveness studies did not disclose the source of costs[16] while three others based costs on national averages rather than on hospital-level data.[17-19] The fifth study lacked detail in describing the intervention and comparator, however primary outcomes were clearly listed and probabilistic sensitivity analysis was performed.[5] Cost summary studies were not critically appraised.[20-24]

The guidelines were generally high in quality. The overall objectives were described in all of the guidelines along with the target population and a link was made between recommendations and supporting evidence. A SR and a description of the evidence were provided, as well as the

methods for formulating the guidelines. Two guidelines excluded patients from participating in the process[25,27] and all did not describe a procedure for updating the guideline.

Summary of Findings

A detailed description of the study findings is provided in Tables A8 and A9 of APPENDIX 4: Main Study Findings and Author's Conclusions.

What is the clinical effectiveness and clinical benefit of endovascular therapy for patients who have undergone ischemic stroke?

The findings of two SRs and seven MAs were mixed. Some results favoured EVT (with or without IV thrombolysis) over IV thrombolysis alone, while others demonstrated that there was no statistically significant difference in performance between the two procedures.

The seven MAs reported on various subsets of nine RCTs (PROACT II, MELT, IMS III, SYNTHESIS EXPANSION, SWIFT PRIME, MR RESCUE, MR CLEAN, EXTEND-IA, and REVASCAT). Three MAs[9,10,12] reported higher rates of favourable outcomes (mRS≤2) in patients treated with EVT compared with those treated with IV thrombolysis or medical management. Four others reported no statistically significant differences in the incidence of favourable outcomes.[3,11,13,14] Five MAs[9,11-14] reported equivalent rates of sICH between EVT and its comparators while one reported a higher (though not statistically significant) incidence in patients treated with EVT.[3] One MA did not report on sICH. The data on mortality rates also were mixed. Five studies[10-14] reported equivalent mortality rates between EVT and the comparators, one reported a higher rate (the statistical significance of the difference was not reported)[3] for EVT, while another reported a lower rate relative to the comparators.[9]

One SR involving studies published between 1997 and 2011 reported a higher rate of sICH in the EVT group but also reported a higher incidence of favourable outcomes.[15] The difference in mortality rate was higher but not statistically significant. The second SR reported that the IMS III and SYNTHESIS EXPANSION studies demonstrated no difference in incidence of favourable outcomes, sICH, or mortality.[1] In four RCTs (i.e. MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME), thrombectomy conducted within six hours of stroke onset proved superior to IV rtPA in terms of incidence of favourable outcomes. The MR CLEAN trial included patients in the Netherlands with proximal artery occlusions randomized to standard medical treatment followed by IA therapy (mostly stent retrievers) (n=233) or standard medical treatment alone (n=267). There was an increased risk of stroke recurrence following EVT. The ESCAPE trial took place in 22 sites in multiple countries and included patients with proximal artery occlusions detected by CTA. Patients were randomized to best medical management (78% to IV rtPA) or IA therapy (86% stent retrievers). The EXTEND-IA trial took place in Australia and patients were selected based on CTP scans.

The authors of one MA suggest that differences in findings between MAs may be related to the increased use of modern stent retrievers over first-generation thrombectomy devices in recently published primary studies and careful selection of patients based on diagnostic imaging examinations.[12] Two MAs were limited to RCTs completed between 2013 and 2015,[9,12] while the remaining studies included RCTs and other types of studies spanning wider ranges of dates up to and including 1990 to 2015.

What is the cost-effectiveness of endovascular therapy for patients who have undergone ischemic stroke?

A cost-effectiveness analysis published in 2013 found that for a hypothetical population of patients treated for ischemic stroke, the ICER of combined IV thrombolysis and IA therapy was €31,687 over IV therapy alone at six months and €1,922 over IA therapy alone over a lifetime.[16] Clinical outcomes of interest were recanalization rates, mRS rates and sICH rates. The analysis compared (1) conservative treatment, (2) IV thrombolysis alone, (3) IA therapy alone, and (4) a combination of IV thrombolysis and IA therapy. Sensitivity analysis demonstrated that for the combined therapy to remain cost-effective, sICH had to remain below 20%.

A cost-utility analysis (CUA) calculated an incremental cost utility ratio (ICUR) of US $14,137 per quality-adjusted life years (QALY) for IA therapy as an adjunct to IV tPA over IV tPA alone within the United States. Inputs for the hypothetical model were extracted from the MR CLEAN RCT and the United States Center for Medicare and Medicaid Services (CMS) database.[17]

Nguyen-Huynh et al. determined that mechanical clot removal or disruption with angioplasty incurred a cost of US $7,718 at a gain of 0.82 QALYs (US $9,386 per QALY) over medical management with antiplatelets and supportive care.[19] Sensitivity analyses demonstrated that the results were dependent on the rates of recanalization. EVT remained cost-effective if recanalization rates were at least 67% and spontaneous recanalization rates for medical management remained below 47%. Changing symptomatic ICH rates between 4% and 14% and increasing Medicare reimbursements by 2.5 had no impact on the cost utility.

The same group of authors reported results from a CUA using data from a systematic literature review, cost data from CMS, and a decision tree for a hypothetical 68 year old patient.[18] Comparing a combination intervention strategy of MET, angiography, and IV tPA with IV tPA alone, the ICUR was reported as US $16,001 per QALY (95% confidence interval, US $2,736-39,232).

In a CUA of radiology equipment, the impact of multimodal CT in evaluating stroke patients for EVT eligibility was assessed.[5] At three months, the ICUR for multimodal CT over noncontrast CT was US $429,000 per QALY. Over a lifetime the ICUR decreased to US $257,250 per QALY, but multimodal CT remained the dominant strategy.

What are the costs and equipment requirements associated with the diagnostics before and during endovascular therapy, specifically regarding computed tomography angiography and magnetic resonance angiography?

Factors influencing hospital costs included treatment type, baseline NIHSS, time to tPA, age, stroke location and comorbid diabetes.[22] Higher costs were associated with higher NIHSS severity scores, longer time to tPA, older age, right hemispheric location of stroke, and diabetes.

What are the evidence-based guidelines associated with endovascular therapy for patients who have undergone ischemic stroke?

Three evidence-based guidelines were found in the literature. The recommendations associated with EVT for patients who have undergone ischemic stroke are as follows:

The 2012 American College of Chest Physicians (ACCP) Guidelines recommend the use of IV rtPA over non-IV rtPA within 4.5 hours of onset of symptoms and recommends against the use of MET except when patients value the unknown benefits of MET over its known risks.[27]

The Society of NeuroInterventional Surgery in the United States recommends MET for patients presenting within eight hours of stroke onset but outside the window for IV thrombolysis therapy.[25] This 2012 guideline specifically mentions the Penumbra aspiration system and the Concentric MERCI clot retrieval device. Very low quality evidence was available on other endovascular devices.

The update to the Canadian Stroke Best Recommendations for Hyperacute Stroke Guidelines added new recommendations for the use of EVT for patients with AIS primarily based on data from five RCTs published in 2014 and 2015.[26] Of note was the recommendation that EVT should be limited to advanced stroke centres. EVT is recommended in patients with a proximal occlusion in the anterior circulation and IA therapy is recommended for those presenting within six hours of onset of symptoms.

References to consensus statements that do not meet the criteria for evidence-based guidelines are found in APPENDIX 5 – Articles of Potential Interest.

Limitations

The primary limitation in the evidence on the clinical effectiveness is the heterogeneity in configuration of the interventions and comparators among the primary studies that were included in the SRs and MAs. Three analyses pooled data from studies involving MET only in the intervention arm,[1,3,15] while the rest included a variety of EVT techniques with or without IV thrombolysis.[9-14] All but one SR and two MAs[3,10,15] did not specify the location of occlusions.[1,9,11-14] Furthermore, two MAs[9,12] were limited to recently published RCTs while the remaining secondary analyses included primary studies published over wider timeframes. The cost-effectiveness analysis studies similarly varied in timeframes, models, and perspectives.

The cost summary data was not specific to diagnostic imaging and the types of materials included were not consistent across studies.

While majority (18 out of 22) of the studies involved authors from North America, only one study[26] - a guideline - was published by authors based in Canada.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

According to authors of one SR, the differences in findings among SRs and MAs may be related to the increased use of modern stent retrievers over first-generation thrombectomy devices in recently published primary studies and careful selection of patients based on diagnostic imaging examinations.[12]

Although IV thrombolysis remains the first-line treatment for patients presenting within 4.5 hours of onset of AIS symptoms, EVT offers a viable option for patients who present outside this window, are contraindicated to IV thrombolysis, or have large vessel occlusions. Based on the limited evidence, it appears that EVT with IV thrombolysis is cost-effective relative to IV thrombolysis alone in selected patients with AIS.

Multimodal CT and MRI are increasingly being introduced into stroke practice for the purpose of selecting the most appropriate treatment protocol for patients. The costs associated with these imaging modalities and their cost-effectiveness relative to standard care has not been widely studied. Limited evidence suggested that multimodal CT is more cost-effective than noncontrast CT in evaluating patients with AIS.

The guidelines for treating AIS patients published by the Canadian Stroke program[26] are generally consistent with one of the United States-based guidelines.[25]

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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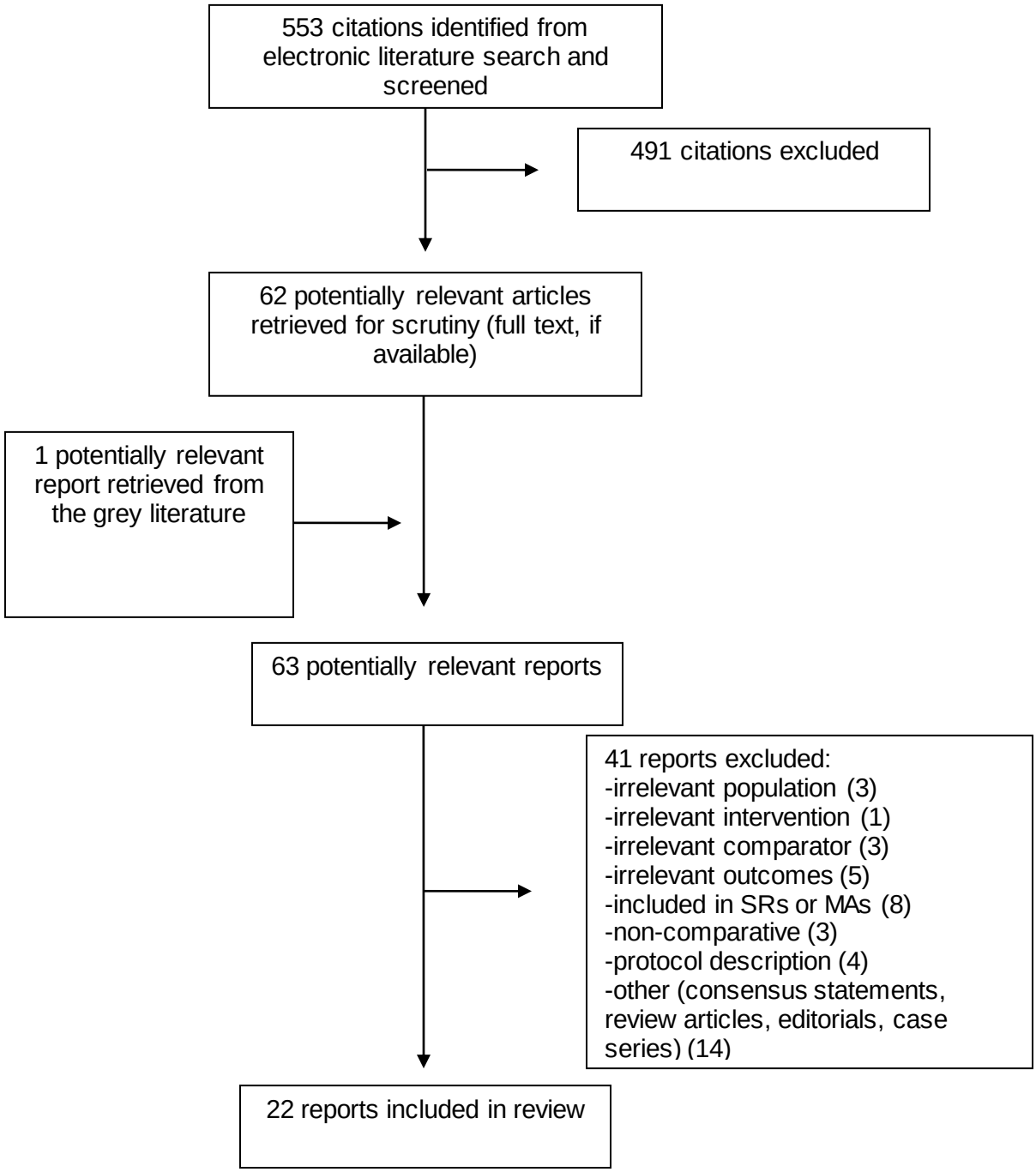
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes Measured
Falk-Delgado[9] 2015 Sweden	MA of 6 RCTs published between 2013 and 2015. The RCTs included were IMS III, MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT.	n=1,569 patients with AIS	(EVT ± IA thrombolysis) + IV tPA	IV tPA (In 3 studies 9% to 22% of patients did not receive IV thrombolysis)	Rate of: mRS sICH Mortality
Fargen[10] 2015 United States	MA of 6 RCTs published between 1999 and 2013 (PROACT II, MELT, IMS III, SYNTHESIS, MR RESCUE, and MR CLEAN)*	n=1,903 patients with LVO	EVT (IA thrombolysis ± thrombectomy)	IV tPA if eligible or IV heparin. Not specified for 57 patients enrolled in MELT RCT.	Rate of: mRS Mortality
Osanai[13] 2015 United States/Peru	MA of 10 RCTs published between 1998 and 2013. Sub-group analysis for MET included 3 RCTs (IMS III, SYNTHESIS, MRRESCUE) published in 2013	n=1,136 in studies involving MET(n=1,612 patients in full study)	MET ± IV/IA tPA (n=679) (in sub-group)	IV tPA or standard care (in sub group)	Rate of: sICH mRS≤2 rate Mortality
Prabhakaran[1] 2015 United States	SR of 9 RCTs, 4 observational studies, guideline statements, and reviews between 1990 and 2015 including IMS III, SYNTHESIS EXPANSION, MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME)	n=108,082 patients	IMS III: IV thrombolysis + MET/IA SYNTHESIS EXPANSION: MET±IA rtPA MR CLEAN: MET ESCAPE:MET/IA + IV rtPA EXTEND-IA: MET + IV rtPA SWIFT PRIME: MET	IV rtPA or other standard care (not described)	Rate of: sICH mRS Mortality

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention**	**Comparator(s)**	**Clinical Outcomes Measured**
Sardar[12] 2015 United States	MA of 8 RCTs published between 2013 and 2015. Data was pooled from the IMS III, MR RESCUE, SYNTHESIS, MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT studies.	n=2,423 patients	EVT + IV tPA	IV tPA	Rate of: mRS sICH Mortality
Lin[11] 2013 China	MA of 5 RCTs published between 2005 and 2013.The analysis included the IMS III RCT, SYNTHESIS (two cohorts) and 2 other RCTs.	n=1,106 patients hospitalized for AIS	IA thrombolysis or EVT ± IV tPA (few stent retrievers were used but authors did not provide details)	IV thrombolysis	Rate of: mRS sICH Mortality (all-cause)
Singh[14] 2013 United States	MA of 5 RCTs published between 2009 and 2013. Studies included the IMS III, SYNTHESIS (two cohorts) and MR RESCUE RCTs.	n=1,197 patients with AIS	EVT ± IV tPA	IV thrombolysis	Rate of: mRS sICH Mortality
Mokin[15] 2012 United States	SR of 1 comparative study and 27 noncomparative studies (21 EVT, 6 IV tPA or heparin) published between 1997 and 2011. This review included 7 noncomparative studies with IV thrombolysis alone and 22 noncomparative studies involving EVT.	n=969 patients with acute ischemic stroke attributable to ICA occlusion	MET, aspiration thrombectomy, stenting, angioplasty, ± IA thrombolysis	IV tPA or IV heparin	Rate of: mRS sICH Mortality
Mullen[3] 2012 United States	MA including 54 case series, non-randomized studies, and RCTs published between 1996 and 2010 (27 prospective, 20 retrospective,	n=5,019 patients with anterior arterial circulation occlusion (90 assigned to MET and 2,450 assigned	MET (guidewire clot maceration, MERCI device, Penumbra device, balloon	IV tPA	Rate of: mRS sICH Mortality

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention**	**Comparator(s)**	**Clinical Outcomes Measured**
	and 7 unidentifiable).	to IV tPA alone). The review also included comparisons with IA chemical thrombolysis alone (1,143 patients), combination of IA chemical and mechanical thrombolysis (819 patients), and IV tPA combined with IA chemical and/or mechanical thrombolysis (293 patients).	angioplasty, and/or stenting)		

AIS = acute ischemic stroke; EVT = endovascular therapy; IA = intra-arterial; IV = intravenous; LVO = large vessel occlusion; MA = meta-analysis; MET = Mechanical Endovascular Therapy; mRS = modified Rankin Scale score; RCT(s) = randomized controlled trial(s); sICH = symptomatic intracerebral hemorrhage; SR = systematic review; tPA = tissue plasminogen activator

* The PROACT and MELT studies did not include mechanical thrombectomy in either arm (n=294)

Table A2: Characteristics of Included Cost-Effectiveness Studies					
First author, Publication Year, Country	**Type of Analysis, Perspective**	**Intervention, Comparator**	**Study Population**	**Time Horizon**	**Main Assumptions**
Leppert[17] 2015 United States	CUA, perspective not reported	IA tPA + IV tPA+ MET versus IV tPA alone	Hypothetical cohort of 65 year old patients with AIS	Lifetime	Non reported
Bouwy[16] 2013 The Netherlands	CEA, patient	IA thrombolysis or combined IA-IV thrombolysis versus conservative therapy or IV thrombolysis. Conservative treatment included a CT scan and best medical care with or without antiplatelet therapy. IV thrombolysis treatment involved a CT scan and rtPA infusion. IA therapy involved a CT scan and a CT angiography scan.	Hypothetical cohort of patients with AIS who are eligible for EVT	6 months post-stroke, lifetime	For IV thrombolysis, recanalization rate = 30% with success rate = 70%. For combined IA-IV thrombolysis, recanalization was estimated at 85%. IA therapy involved retrievable stents in 50% of patients. Costs (in 2010) for hospital care, rehabilitation, nursing home, and home care were €12,617, €12,360, €12,695, and €12,633 for conservative treatment, IV thrombolysis, IA therapy, and combination of IV and IA thrombolysis, respectively. Corresponding lifetime costs were €34,182, €34,182, €32,199, and €32,335, respectively.
Kim[18] 2011 United States	CUA , society	Thrombectomy + IV tPA versus IV tPA	Single, hypothetical 68 year old patient with large vessel occlusion	Lifetime	Recanalization rates = 72.9% for combination strategy and 46.2% for IV tPA. The sICH rates for the combination strategy were 8.6% with recanalization and 15.4% without recanalization (Multi MERCI trial)

Table A2: Characteristics of Included Cost-Effectiveness Studies

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Nguyen-Huynh[19] 2011 United States	CUA , society	Thrombectomy/angioplasty/clot disruption versus medical care (antiplatelets + supportive care	Hypothetical cohort of 65 year old patients with AIS and occlusion of a major intracranial artery presenting after 3 hours of stroke onset	3-6 months post-stroke	ICH rate equivalent to that in the control arm of PROACT II study. Recanalization with mechanical intervention = 84%; sICH rate = 6.3%. For medical management, a sICH rate of 2% was associated with a spontaneous recanalization rate of 24% while a sICH rate of 5.5% was used for patients in whom recanalization was not successful.
Young[5] 2010 United States	CUA, payer	Multimodal CT (including noncontrast CT, contrast-enhanced CT, CT angiography, and CT perfusion) versus noncontrast CT followed by conventional angiography	Hypothetical cohort of stroke patients presenting within 3 hours of stroke with intraluminal thrombuses that could be treated with IA procedures	3 months, lifetime	Costs in 2008 US $ 20% of patients were contraindicated to IV tPA and IA Single stroke events Markov model Outcome values from a 2004 MA, the PENUMBRA Post and Multi MERCI trials..

ADAPT = A Direct Aspiration First Pass Technique; AIS = acute ischemic stroke; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; CT = computed tomography; EVT = endovascular therapy; IA = intraarterial; ICER = incremental cost-effectiveness ratio; IV = intravenous; LOS = length of stay; PENUMBRA = Penumbra aspiration system with separator; RCT(s) = randomized controlled trial(s); sICH = symptomatic intracranial/intracerebral hemorrhage; SRLA = stent retriever with local aspiration; tPA = tissue plasminogen activator; MET = mechanical thrombectomy

Table A3: Characteristics of Included Cost Summary Studies					
First author, Publication Year, Country	**Cost parameters, Perspective**	**Intervention, Comparator**	**Study Population**	**Time Horizon**	**Costs**
Simpson[22] 2014 United States	Estimated mean cost to the patient between August 2006 and April 2012	IV tPA + EVT versus IV t-PA alone	430 (out of 454) patients with AIS enrolled in the IMS III RCT	Not reported	EVT: US $35,130 IV-rtPA: US $25, 630
Turk[23] 2015 United States	Mean direct and indirect costs and benefits to the patient at a single centre between May 2008 and October 2012. Device costs included femoral sheaths, IA tPA, guidewires, catheters, aspiration devices, and devices such as balloons, stents, or any other adjuvant devices used to treat complications.	MET with ADAPT versus MET with PENUMBRA or SRLA	171 patients with AIS	Duration of stay	Penumbra aspiration system with separator: US $11,158.62 (range US $3,296.00 - US $60,872.91) Trevo PRO or Penumbra 3D separator stent retriever devices: US $16,021.53 (range US $9,601.85 – US $35,724.00)
Turk[24] 2014 United States	Mean cost of hospitalization to patients between January 2009 and December 2013 at a single centre.	MET with PENUMBRA versus MET with stent retrievers	222 patients with AIS	Duration of stay	Overall cost: US $46,832 PENUMBRA (128 patients): US $51,599.16±US $31,325.77 SRLA (30 patients): US

Table A3: Characteristics of Included Cost Summary Studies

First author, Publication Year, Country	Cost parameters, Perspective	Intervention, Comparator	Study Population	Time Horizon	Costs
					$54,699.94±US $29,623.93 ADAPT (64 patients): US $33,610.75±US $17,126.66
Brinjikji[21] 2011 United States	Median patient costs between 2006 and 2008 based on the United States National Inpatient Sample database	Embolectomy versus no Comparator	Patients with ischemic stroke, undergoing endovascular clot removal between 2006 and 2008	Duration of stay or death	US $$36,999 for good outcomes; US $35,109 for patients who died and US $50,628 for patients with morbidity. All costs were related to stroke event
Bing[20] 2013 France	Provider costs. EVT materials (stroke devices, wires, catheters, femoral introducers, carotid stents, and recombinant tissue plasminogen activator) between November 2009 and July 2011	MET/IA thrombolysis without a comparator	57 patients with AIS and occlusion in the anterior circulation	3 months	Average cost of equipment = €5,018±2402. Excluded specialist salaries

ADAPT = A Direct Aspiration first Pass Technique; PENUMBRA = Penumbra aspiration system with separator; SRLA = stent retriever with local aspiration

Table A4: Characteristics of Included Evidence-Based Guidelines and Statements

Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
Casaubon, 2015[26] – Heart and Stroke Foundation of Canada						
Healthcare professionals/Patients with TIA, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, or acute venous sinus thrombosis	MET for AIS	Not reported	Systematic literature search, data extraction, and quality of evidence determined through consensus	CSBPR methodology	Process adapted from the Practice Guideline Evaluation and Adaptation Cycle. Guidelines drafted, reviewed, and revised recommendation statements by interprofessional group of stroke experts	Peer review for level C recommendations
Blackham, 2012[25] – Society of NeuroInterventional Surgery						
Patients with AIS	EVT for AIS	Rate of: Recanalization Functional independence	AHA 2007 Guidelines for the early management of adults with ischemic stroke, scientific statement indications. SR of the literature	AHA, CEBM levels of evidence	Recommendations were developed based on guidelines for evidence based medicine proposed by the Stroke Council of the AHA and the University of Oxford, CEBM	Reviewed by SNIS Executive Committee. No external peer review.

Lansberg, 2012[27] – American College of Chest Physicians						
Clinicians treating patients who have had ischemic stroke	Antithrombotic and thrombolytic therapy for ischemic stroke	mRS score ≤ 2, all-cause mortality, nonfatal cardiac events	SR, MAs, quality of evidence assessed with GRADE methodology	GRADE system	Recommendations incorporated patients' values	External review based on the GRADE system

ACC = American College of Cardiology; AHA = American Heart Association; AIS = acute ischemic stroke; CEBM = Centre for Evidence Based Medicine; CSBPR = Canadian Stroke Best Practice Recommendations; CT = computed tomography; CTA = CT angiography; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; LOE = level of evidence; NICE = National Institute for Clinical Excellence; SNIS = Society of NeuroInterventional Surgery; rtPA = recombinant tissue plasminogen activator; TIA = transient ischemic attack; tx = therapy/treatment

APPENDIX 3: Critical Appraisal of Included Publications

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using Amstar[6]

First Author, Publication Year	Strengths	Limitations
Falk-Delgado[9] 2015	• There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • The status of publication was an inclusion criterion. • A list of studies (included and excluded) was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented • The scientific quality of the included studies was used appropriately in formulating conclusions. • Appropriate methods were used to combine the findings of the studies. • The likelihood of publication bias was addressed. • Authors declared that they had no conflict of interest. • Study designs were limited to RCTs.	• An 'a priori' design was not provided.
Fargen[10] 2015	• There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • The status of publication was an inclusion criterion. • A list of included studies was provided. One excluded study was identified by name. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented • The scientific quality of the included studies was used appropriately in formulating conclusions. • Appropriate methods were used to combine the findings of the studies. • Conflict of interest for the reviewers was considered.	• An 'a priori' design was not provided. • The likelihood of publication bias was not addressed. • Three of six authors declared conflicts of interest.

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using Amstar[6]		
First Author, Publication Year	**Strengths**	**Limitations**
	• Study designs were limited to randomized controlled trials.	
Osanai[13] 2015	• There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • The status of publication was an inclusion criterion. • A list of studies (included and excluded) was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented • The scientific quality of the included studies was used appropriately in formulating conclusions. • Appropriate methods were used to combine the findings of the studies. • The likelihood of publication bias was addressed with Egger's test. • Authors declared there were no competing interests. • Study designs were limited to randomized controlled trials.	• An 'a priori' design was not provided.
Prabhakaran[1] 2015	• There was duplicate study selection and data extraction. • The status of publication was an inclusion criterion. • A list of included was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented • The scientific quality of the included studies was used appropriately in formulating conclusions. • Conflict of interest for the reviewers was considered. • Study designs were limited to randomized controlled trials.	• An 'a priori' design was not provided. • The MEDLINE database was the only one searched. • Excluded studies were not discussed. • Narrative summary of findings were provided. • The likelihood of publication bias was not addressed.

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using Amstar[6]

First Author, Publication Year	Strengths	Limitations
Sardar[12] 2015	• There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • A list of included studies was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented • The scientific quality of the included studies was used appropriately in formulating conclusions. • Appropriate methods were used to combine the findings of the studies. • The likelihood of publication bias was addressed. • The reviewers indicated that there were no conflicts of interest. • Only randomized controlled trials were included.	• An 'a priori' design was not provided. • The status of publication was not an inclusion criterion.
Lin[11] 2013	• There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • A list of studies (included and excluded) was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented • The scientific quality of the included studies was used appropriately in formulating conclusions. • Appropriate methods were used to combine the findings of the studies. • The likelihood of publication bias was addressed. • Conflict of interest for the reviewers was considered. • Study designs were limited to randomized controlled trials.	• An 'a priori' design was not provided.

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using Amstar[6]

First Author, Publication Year	Strengths	Limitations
Singh[14] 2013	• An 'a priori' design was registered. • There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • A list of studies (included and excluded) was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented • The scientific quality of the included studies was used appropriately in formulating conclusions. • Appropriate methods were used to combine the findings of the studies. • The authors stated that publication bias was not assessed because fewer than 10 studies were included. • Study designs were limited to randomized controlled trials.	• The status of publication was not an inclusion criterion. • Conflict of interest for the reviewers and individual studies was not discussed.
Mokin[15] 2012	• A comprehensive literature search was performed. • The status of publication was an inclusion criterion. • A list of studies (included and excluded) was provided. • The characteristics of the included studies were provided. • Appropriate methods were used to combine the findings of the studies.	• An 'a priori' design was not provided. • Study selection and data extraction was not described. • The scientific quality of the included studies was not assessed. • The likelihood of publication bias was not addressed. • Conflict of interest for the reviewers and individual studies was not discussed.

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using Amstar[6]

First Author, Publication Year	Strengths	Limitations
Mullen[3] 2012	• There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • The scientific quality of the included studies was assessed and documented • Appropriate methods were used to combine the findings of the studies.	• An 'a priori' design was not provided. • The status of publication was not part of the inclusion criteria. • A list of studies (included and excluded) was provided. • Aggregated data was used in the analysis rather than patient-level data. • The likelihood of publication bias was not addressed. • Conflict of interest for the reviewers and individual studies was not discussed.

RCT(s) = Randomized Controlled Trial(s)

Table A6: Strengths and Limitations of Economic Studies using Drummond'		
	Strengths	**Limitations**
Young[5] 2010	• A probabilistic sensitivity analysis was performed. • The primary outcome measures are clearly stated. • The comparator is consistent throughout the study • Assumptions are described. • Based on data from clinical trials.	• The intervention and comparator are not described in detail.
Kim[18] 2011	• The intervention and comparator are clearly defined. • The form of economic evaluation is accurately stated. • A detailed decision tree model is provided. • The approach to sensitivity analysis is clearly described. • Listed outcomes of interest.	• Costs are based on national averages not on hospital-level databases.
Nguyen-Huynh[19] 2011	• The intervention and comparator are clearly defined. • The approach to sensitivity analysis is clearly described. • A detailed decision tree model is provided. • The time horizon of costs and benefits is stated.	• Costs are based on national averages not on hospital-level databases.
Bouvy[16] 2013	• The intervention and comparator are defined. • The approach to sensitivity analysis is described. • A detailed decision tree model is provided. • The time horizon of costs and benefits is stated.	• Source of costs is not disclosed.
Leppert[17] 2015	• The intervention and comparator are defined. • Primary outcome measures are provided. • The approach to sensitivity analysis is described. • A detailed decision tree model is provided. • Method for calculating costs is described. • The discount rate is stated. • The time horizon of costs and benefits is stated.	• Costs are based on national averages not on hospital-level databases.

Table A7: Strengths and Limitations of Guidelines using AGREE II[8]		
	Strengths	**Limitations**
Casaubon[26] 2015	• The overall objectives of the guideline are described. • The health questions covered by the guideline are described. • The patients to whom the guideline is meant to apply are described. • Members of the guideline development group include stroke neurologists, ED physicians, neurosurgeons, radiologists, family physicians, paramedics, nurses, stroke program managers, physiotherapists, occupational therapists, a speech language pathologist, a social worker, and a stroke survivor. • Survivors of stroke or their family members are included as writers and/or external reviewers. • The target users of the guideline are defined as all healthcare professionals involved in the care of patients with stroke or transient ischemic attacks. • Systematic methods were used to search for evidence. • The criteria for selecting the evidence are described. • The strengths and limitations of the body of evidence are described. • The methods for formulating the recommendations are described. • The health benefits, side effects, and risks have been considered in formulating the recommendations. • There is an explicit link between the recommendations and the supporting evidence. • The guideline has been externally reviewed by experts prior to its publication.	• A procedure for updating the guideline is not provided.
Blackham[25] 2012	• The overall objectives of the guideline are described. • The patients to whom the guideline is meant to apply are described. • Members of the guideline development group are affiliated with departments Radiology, Neurological Surgery, neurology, and Neuroradiology. • Systematic methods were used to search for	• The guidelines do not appear to have been developed with input from patients. • The target users of the guideline are not clearly defined • The criteria for selecting the evidence were not clearly described. • The methods for formulating the recommendations

Table A7: Strengths and Limitations of Guidelines using AGREE II[8]		
	Strengths	**Limitations**
	evidence. • The strengths and limitations of the body of evidence are described. • The health benefits, side effects, and risks have been considered in formulating the recommendations. • There is an explicit link between the recommendations and the supporting evidence.	were not clearly described. • The guideline was developed by experts from multiple institutions; however there is no indication that an external review was done by individuals other than those within the development group. • The document does not present a process for updating the guideline
Lansberg[27] 2012	• The overall objectives of the guideline are described. • The health questions covered by the guideline are specifically described. • The guideline addresses three sub-populations of patients with stroke. • Members of the guideline development group are affiliated with departments of Neurology and Neurological Sciences, Epidemiology and Biostatics, Medical Schools, and Research Centres. • The target users of the guideline are physicians treating patients who have had an ischemic stroke • Systematic methods were used to search for evidence. • The strengths and limitations of the body of evidence are described. • The methods for formulating the recommendations are described. • The health benefits, side effects, and risks have been considered in formulating the recommendations. Remarks were added to each recommendation addressing special patient cases. • There is an explicit link between the recommendations and the supporting evidence. • The guideline has been externally reviewed by experts prior to its publication.	• Patients were not consulted in the guideline development process. • The criteria for selecting the evidence were not described. • A procedure for updating the guideline is not provided.

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A8: Summary of Findings of Systematic Reviews and Meta-analyses

Main Study Findings		Author's Conclusions
First Author, Publication Year, Country	**Main Study Findings**	**Author's Conclusions**
Falk-Delgado[9] 2015 Sweden	Clinical outcomes (intervention [n=824] versus comparator [n=745]): mRS≤2 rate: 46% versus 27% (*P*<0.00001) sICH rate: 41% versus 34%, *P*=0.85 Mortality rate: 15% versus 20% (*P*=0.02; difference not apparent after sensitivity analysis)	"Patients with acute stroke treated with IV thrombolysis and additional endovascular treatment with mechanical thrombectomy show improved functional outcome and lower mortality after 3 months from stroke onset compared with patients receiving IV thrombolysis alone." (p 6)[9]
Fargen[10] 2015 United States	Clinical outcomes (intervention [n=655] versus comparator [n=528]): mRS≤2 rate: 38.3% versus 25.8% (*P*=0.0001) Mortality: 18.6% versus 21.6% (*P*=0.13)	The results "demonstrate superior outcomes in subjects with LVO receiving EVT compared with medical management". (p 89)[10]
Osanai[13] 2015 United States/Peru	Clinical outcomes (intervention [n=679] versus comparator [n=457]): mRS≤2 rate: 39% versus 39.6% (*P*=0.83) sICH rate: 5.9% versus 5.5% (*P*=0.83) Mortality rate: 17.8% versus 17.3% (*P*=0.90)	"…mechanical device usage was not associated with increase in good outcome in terms of disability… In general there were no differences in subgroup analyses when compared with the main analyses" for mortality and sICH. (p 8)[13]
Prabhakaran[1] 2015 United States	Listed results from RCTs	"..early trials using first-generation approaches [to mechanical thrombectomy] failed to show clinical benefit despite successful recanalization rates" "Intravenous rtPA remains the standard of care for patients with moderate to severe neurological deficits who present within 4.5 hours of symptom onset. Outcomes for some patients with acute ischemic stroke and moderate to severe neurological deficits due to proximal artery occlusion are improved with endovascular reperfusion therapy. Efforts to hasten reperfusion therapy, regardless of the mode, should be undertaken within organized stroke systems of care." (p 1461)[1]

Table A8: Summary of Findings of Systematic Reviews and Meta-analyses		
Main Study Findings		**Author's Conclusions**
First Author, Publication Year, Country	**Main Study Findings**	**Author's Conclusions**
Sardar[12] 2015 United States	Clinical outcomes (intervention [n=633] versus comparator [n=650]): mRS≤2 rate: 42.4% versus 31.7% (odds ratio of 1.73 with 95% CI 1.18-2.53) sICH rate: 5.1% (out of 634) versus 4.8% (out of 653) (odds ratio of 1.07 with 95% CI 0.73- 1.56) Mortality (all-cause) rate:16.2% versus 17.3% (odds ratio of 0.89 with 95% CI 0.68-1.15)	"EVT significantly improved functional outcomes in a selected group of patients with acute large-vessel [ischemic] strokes. Proper patient selection to identify large-vessel occlusions with limited completed stroke volumes using CTA with or without perfusion imaging is critical to treatment success. Use of modern stent-retriever devices during procedures achieving high rates of complete or near complete revascularization may provide additional safety and efficacy" (p 7)[12]
Lin[11] 2013 China	Clinical outcomes (intervention [n=634] versus comparator [n=438]): mRS≤2 rate: 43.06% versus 41.78% (*P*=0.52) sICH rate: 6.25% (out of 656) versus 6.22% (out of 450) (*P*=0.91) Mortality (all-cause) rate: 8.45% versus 17.35% (*P*=0.99)	Results suggest "that endovascular therapy may produce similar good and excellent clinical outcomes, symptomatic hemorrhage and mortality as compared with intravenous thrombolysis in acute ischemic stroke". (p 5)[11]
Singh[14] 2013 United States	Clinical outcomes (intervention [n=163] versus comparator [n=108]): mRS≤2 rate: 40% versus 39.5% sICH rate: 5.9% versus 6.1% Mortality rate: 18% versus 17.1%	"This meta-analysis failed to show any superiority of EVTT over IV tPA for patients with AIS. EVT may lead to a better outcome for patients with severe strokes; however, these results should be interpreted with caution and need to be confirmed in a double-blind, large, multicenter RCT." (p 6)[14]
Mokin[15] 2012 United States	Clinical outcomes (intervention [n=193] versus comparator [n=338]): mRS≤2 rate: 33.6% versus 24.9% (*P* =0.004) sICH rate: 11.1% versus 4.9% (*P*=0.001) Mortality rate: 32% versus 27.3% (*P*=0.12)	Results suggest that "an endovascular approach in treating strokes with ICA occlusion results in overall better clinical outcomes, when compared to systemic thrombolysis alone" (p 2366)[15]

Table A8: Summary of Findings of Systematic Reviews and Meta-analyses		
Main Study Findings		**Author's Conclusions**
First Author, Publication Year, Country	**Main Study Findings**	**Author's Conclusions**
Mullen[3] 2012 United States	Clinical outcomes (intervention versus comparator): Average mRS score: 4.0 versus 3.2 sICH rate: 7.8% versus 7.0% Mortality rate: 40% versus 17.5%	"After accounting for baseline differences between studies, there was no statistically significant difference between treatment groups in functional outcome. This study supports the need for further research [involving RCTs] investigating the role of EVTs for AIS." (p 2354)[3]

AIS = acute ischemic stroke; CI = confidence interval; EVT = endovascular therapy; IA = intra-arterial; ICA = intracranial artery; IV = intravenous; LVO = large vessel occlusion; MET = Mechanical Endovascular Therapy; mRS = modified Rankin Scale score; RCT(s) = randomized controlled trial(s); sICH = symptomatic intracerebral hemorrhage; SR = systematic review; tPA = tissue plasminogen activator

Table A9: Summary of Findings of Economic Studies		
Main Study Findings		**Author's Conclusions**
First Author, Publication Year, Country	**Main Study Findings**	**Author's Conclusions**
Leppert[17] 2015 United States	IA therapy resulted in a gain of 0.7 QALY for an additional cost of US $9911 (i.e. US $14,137 per QALY). Multivariable sensitivity analysis predicted cost-effectiveness (≤$50,000 per QALY) in 97.6% of simulation runs	"IA therapy [in addition to IV thrombolysis] is likely cost effective for patients with anterior circulation strokes and proximal occlusion within six hours of stroke onset." (p 1875).[17] The authors add that diagnostic imaging may prove useful as an adjunct in determining patient eligibility for additional treatment following initial IV thrombolysis.
Bouvy[16] 2013 The Netherlands	ICER of combined IV thrombolysis and IA therapy over IV therapy alone at 6 months = CAD46,421 (€31,687) ICER of combined IV thrombolysis and IA therapy over IA therapy alone over a lifetime = CAD2816 (€1922)	The authors conclude that in order to EVT to become accepted in clinical practice, costs, and rates of sICH, good outcomes and recanalization must meet estimates used in this study.
Kim[18] 2011 United States	ICUR of the intervention over the comparator = US $16 001 per QALY (95% CI, US $2736–US $39 232 per QALY)	"Interventional treatment strategies with adjunctive MET or intra-arterial thrombolysis appear to have an acceptable cost-effectiveness profile compared to IV tPA alone for large-vessel stroke" (p 2017)[18]
Nguyen-Huynh[19] 2011 United States	Net ICUR of the intervention over the comparator = US %9386 per QALY	Results suggest that MET may be cost-effective relative to the best medical therapy in patients with large artery occlusion.
Young[5] 2010 United States	The ICUR for multimodal CT over noncontrast CT is US $429,000/QALY 3 months following EVT for AIS	"Multimodal CT is a cost-effective screening tool for individuals presenting with an acute stroke who would be considered for IV tPA or IA procedures" (p 249)[5]

CT = computed tomography; EVT = endovascular therapy; IA = intraarterial; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio IV = intravenous; MET = mechanical thrombectomy; QALY = quality life-adjusted year; RCT(s) = randomized controlled trial(s); sICH = symptomatic intracranial/intracerebral hemorrhage; tPA = tissue plasminogen activator

APPENDIX 5: Articles of Potential Interest

Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al. 2015 AHA/ASA focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015 Jun 29. [Epub ahead of print].

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Wintermark M, Luby M, Bornstein NM, Demchuk A, Fiehler J, Kudo K, et al. International survey of acute Stroke imaging used to make revascularization treatment decisions. Int J Stroke. 2015 Jul;10(5):759-62.

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