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Number 127

Acute Stroke: Evaluation and Treatment

Prepared for:
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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850 or by e-mail to **epc@ahrq.gov.**

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Acknowledgments

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Structured Abstract

Context: Stroke defines an acute vascular event in the brain and is a leading cause of death and disability. Ischemic stroke results from decreased blood flow to a portion of the brain with consequent cell death. Hemorrhagic stroke, on the other hand, is a result of bleeding into the brain. Ischemic stroke is far more common and is potentially treatable with thrombolytic therapy. While effective, the wide application of this therapy has been hampered by restrictive selection criteria based on time since onset of symptoms. Successful treatment requires a system capable of rapidly identifying and evaluating prospective candidates. In this context, use of community education, specific ED protocols and designated treatment centers may demonstrate some advantages. Evidence is emerging that patient selection by time since stroke onset, imaging characteristics, and intra-arterial treatment may increase the probability of recanalization of occluded vessels. Normalization of serum glucose, acute blood pressure management and surgical extraction of intracerebral clot may be of benefit in some circumstances.

Objectives: The purpose of this report is to systematically review the available literature in the field of acute stroke evaluation and treatment. The University of Ottawa Evidence-based Practice Center (UO-EPC) task involving the following three areas: (1) what interventions in acute stroke (<24 hours from onset) are effective in reducing morbidity and mortality (2) how safety and effectiveness of these interventions vary by timing in relation to onset of symptoms and (3) determine what the evidence is that specific systems of care improve outcomes of acute stroke.

Data Sources: The databases searched were MEDLINE® (1966 to April Week 4 2004), Embase (last 6 months) and CINAHL (1982 to April Week 5 2004) using the OVID interface. Also searched were the Stroke Trials Directory, the Cochrane Stroke Group Registry, conference proceedings from the 28th International Stroke Conference 2003 (*Stroke*, Feb 2004) and the American Academy of Neurology Annual Meeting (published in *Neurology*). The Effective Practices and Organization of Care (EPOC) registry was searched by the Cochrane review group.

Study Selection: All results of searches for evidence were provided to two reviewers for assessment. All studies were screened by both reviewers by reviewing the bibliographic records, and when meeting inclusion criteria, the subsequent full-text of the record. If the reviewers did not agree in finding at least one unequivocal reason for excluding the study, it was entered into the next phase of the review. The reasons for exclusion were noted using a modified QUOROM format.

Data Extraction: Two reviewers independently abstracted the contents of each included study using an electronic Data Abstraction form developed especially for this review. Data abstracted included the study and population characteristics, intervention characteristics and relevant outcomes of included studies.

Data Synthesis: Attempts were made to minimize, and where not possible, explain statistical and clinical heterogeneity. Pooled estimates were only calculated if clinically and statistically appropriate. In situations where it was felt to that quantitative synthesis could not be performed, a qualitative narrative synthesis was conducted.

Results/ Conclusions: Currently, available data do not support a role for surgery in the treatment of acute intracerebral hemorrhage. Results, however, do not preclude benefit from surgery which involves modalities other than those studied in the acute trials (e.g., minimally invasive technologies) or treatment of hemispheric hematoma at very early timeframes. Further, the available literature did not comment on cerebellar hematoma and thus this analysis does not apply to infratentorial hemorrhage.

In spite of potential importance, availability of therapy and ease of administration of antihypertensive agents, very little data exists to suggest that their use is of benefit (or results in harm) in the setting of acute ICH. A similar situation exists regarding glucose management for acute ischemic stroke. Further studies are required in both these areas.

IV thrombolysis with tPA is effective and efficacious for acute ischemic stroke within 3 hours of symptom onset. The effectiveness is strongly linked to time since onset of symptoms with shorter times demonstrating significantly better outcomes. Patient level meta-analysis suggests that treatment may be effective up to 270 minutes with treatment increasing the odds of death beyond 270 minutes. Further work is needed to define the risks and benefits of treatment outside the 3 hour window prior to advocating widespread use in these patients. Intra-arterial therapy remains an option for a subgroup of patients with large vessel occlusions principally in the middle cerebral artery distribution. The evidence for this intervention, however, remains less robust than for IV therapy. Limited data is available regarding patient characteristics predicting outcome. The system changes required to ensure prompt delivery of appropriate therapy are complex and operate on multiple levels. In spite of their critical role, little data exists regarding the efficacy of these interventions and, in particular, the relative efficacy of various components with regard to patient outcomes.

Ultrasound for enhancement of thrombolysis in the setting of MCA occlusion has suggested efficacy in 2 studies and a definitive trial to demonstrate the benefit and risks is required.

CT and MRI imaging for patient selection and prediction of outcome in thrombolysis has yet to be prospectively evaluated. The two included CT studies differ in onset to evaluation time with only a weak correlation between CT changes and outcome seen in the trial enrolling patients from 0-6 hours. Neither study quantified CT changes. The ASPECTS score is an easily quantifiable scoring system for early infarct changes. Retrospective evaluation of the ASPECTS score suggests that values below 7 correlate with poorer outcomes. As CT is widely available this system deserves further exploration. Additional information relevant to treatment decisions may be provided by CT angiography. Occlusion of proximal vessels is associated with higher rates of infarction and thus may influence treatment modalities.

MRI DWI lesions correlate with the presence of infarcts in small cohorts of patients and time to peak measures on early scans may correlate with recanalization after IV tPA treatment. These findings require reproduction and further evaluation. The multiplanar abilities and potential for acquisition of multiple parameters are potentially attractive features of this modality and may assist in selecting patients with a greater ratio of benefit to harm in intravenous and intra-arterial treatment paradigms.

The narrow time window for thrombolysis in acute stroke as well as the relationship between time to treatment and outcome has led to the exploration of a number of strategies for optimization of outcomes. Community education programs regarding the symptoms of stroke have not been independently evaluated but rather studied in the context of more comprehensive system changes. Thus it is unclear if these programs are effective in improving patient outcomes. Further exploration is also required regarding the content and targeting of such programs. Descriptions of designated treatment centers have shown the feasibility of this approach but an evaluation of published criteria for and marginal effectiveness of such designations remains to be performed.

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Acute Stroke: Evaluation and Treatment

Summary

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Introduction

Stroke defines an acute vascular event in the brain and is a leading cause of death and disability. Ischemic stroke results from decreased blood flow to a portion of the brain with consequent cell death. Hemorrhagic stroke, on the other hand, is a result of bleeding into the brain. Ischemic stroke is far more common and is potentially treatable with thrombolytic therapy. While effective, the wide application of this therapy has been hampered by restrictive selection criteria based on time since onset of symptoms. Successful treatment requires a system capable of rapidly identifying and evaluating prospective candidates. In this context, use of community education, specific ED protocols and designated treatment centers may demonstrate some advantages. Evidence is emerging that patient selection by time since stroke onset, imaging characteristics, and intra-arterial treatment may increase the probability of recanalisation of occluded vessels. Normalization of serum glucose, acute blood pressure management and surgical extraction of intracerebral clot may be of benefit in some circumstances.

The purpose of this report is to systematically review the available literature in the field of acute stroke evaluation and treatment. The task of the University of Ottawa Evidence-based Practice Center (UO-EPC) involved the following three areas: (1) What interventions in acute stroke (<24 hours from onset) are effective in reducing morbidity and mortality? (2) How do safety and effectiveness of these interventions vary by timing in relation to onset of symptoms? (3) What is the evidence that specific systems of care improve outcomes of acute stroke?

Methods

The databases searched were MEDLINE® (1966 to April Week 4 2004), EMBASE (last 6 months) and CINAHL® (1982 to April Week 5 2004) using the OVID interface. Also searched were the Stroke Trials Directory, the Cochrane Stroke Group Registry, conference proceedings from the 28th International Stroke Conference 2003 (*Stroke,* February 2004) and the American Academy of Neurology Annual Meeting (published in *Neurology*). The Effective Practices and Organization of Care (EPOC) registry was searched by the Cochrane review group.

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especially for this review. Data abstracted included the study and population characteristics, intervention characteristics and relevant outcomes of included studies.

Attempts were made to minimize and, where not possible, explain statistical and clinical heterogeneity. Pooled estimates were only calculated if clinically and statistically appropriate. In situations where it was felt that quantitative synthesis could not be performed, a qualitative narrative synthesis was conducted.

Results

Intervention A

Does surgery impact the outcome in patients with acute intracerebral hematoma? Twenty-three studies were identified by our search. Meta-analysis was conducted on four studies. The four trials had a total of 246 subjects. The pooled estimate favored treatment; however, the confidence interval crossed the null (OR=0.24 [0.02, 3.03]). A meta-analysis for the outcome of death produced similar results (OR=0.62 [0.34, 1.13]). The meta-analysis was repeated including the study published after the period included in the search strategy. This study had significantly greater numbers than the other included studies; however, the conclusion of the meta-analysis was not altered. Once again, the odds ratio for death had a point estimate favoring treatment; however, the confidence interval clearly crossed the null (OR=0.81 [0.54, 1.22]). Moderate heterogeneity was noted.

Intervention B

Does antihypertensive treatment reduce stroke-related mortality and disability in patients with acute intracerebral hemorrhage (ICH)? Six studies were identified that investigated antihypertensive therapy for ICH. Four of these were non comparative case series and thus were excluded from our review. Two unique studies met eligibility criteria and were pre- and post-designs. Neither study commented on outcomes of death or disability. One suggested that cerebral perfusion pressure was not altered with antihypertensive therapy.

Intervention C

Does intra-arterial (IA) thrombolysis reduce stroke-related mortality and disability in adults with acute ischemic stroke? Of the 37 studies identified by the search strategy, five unique publications met criteria for inclusion. Two studies could be combined with the pooled estimates for death and disability and death favoring treatment with a confidence interval which crossed the null in both cases: death and disability (OR=0.55 [0.29, 1.16]), and death (OR=0.78 [0.42, 1.47]). Thus, while the pooled estimates for these outcomes are not statistically significant the possibility of substantial benefit from intra-arterial therapy cannot be excluded. A pooled estimate of the impact on disability alone could not be obtained from the available data. A single study[1] suggests an absolute improvement in the proportion of subjects with a mRS score < or = 2 of 15 percent. The odds ratio for this outcome was 2.13 (1.02, 4.42).

Intervention D

Does treatment to normalize blood glucose levels reduce stroke-related mortality and disability in adults with acute stroke? No studies were identified which specifically addressed this question. Two unique publications demonstrated the feasibility of reduction in serum glucose levels but were not designed to measure clinical outcome.

Intervention E

Does mechanical clot disruption reduce stroke-related mortality and disability in adults with acute ischemic stroke? Ten studies were identified by the search criteria and one, which fell outside the search dates, was provided by an expert. Of these, two unique RCTs met the criteria for inclusion. Both evaluated the effect of ultrasound enhanced thrombolysis in middle cerebral artery (MCA) occlusion. Primary end points differed but the treatment effect in both studies favored intervention.

Intervention F

Is the effectiveness and safety of thrombolytic therapy for adults with acute ischemic stroke affected by time from onset to treatment? No single study has attempted to investigate the impact of timing on thrombolysis treatment outcome. However, five unique publications examining treatment outcomes across relevant time windows were included.[2]

Studies examining enrollment of patients 3 to 5 hours after stroke onset and 0 to 6 hours after onset did not show treatment benefit.[2,3] Reanalysis of the NINDS trial data[4] suggested improved functional outcome for the 0-90 minute stratum as compared with the 91-180 minute interval. A patient level meta-analysis of six trials of tPA treatment for ischemic stroke with treatment windows between 0 and 6

hours was identified which examined the relationship between onset to treatment time and outcome.[5] A clear association was found between onset to treatment time and outcome. The odds ratio for favorable outcome with tPA treatment in the 0 to 90 minute interval was 2.81 (95% CI 1.75-4.50). This decreased to 1.15 (0.90-1.47) in the 271 to 360 minute interval. No increase in mortality was noted until the 271-360 minute interval.

Intervention G

Do pretreatment CT scoring systems affect the safety and efficacy of thrombolytic therapy for acute ischemic stroke? Two unique studies were included in this analysis.[6] Prospective evaluation of CT scoring systems was not available, and both included studies are evaluations of CTs conducted during the course of prospective trials of thrombolysis in stroke. Analysis of CT scans from patients in the NINDS trial demonstrates that while early infarct changes are common, they correlate poorly with outcome.[6] A weak association between early CT changes and outcome was noted in the PROACT 2 trial.[7]

Intervention H

Do pretreatment MRI scoring systems affect the safety and efficacy of thrombolytic therapy for acute ischemic stroke? Six studies were identified that addressed the effectiveness of an MRI scoring system for ischemic stroke. One multiple prospective cohort study[8] and one single prospective cohort study,[9] published in 2002 and 2003, were included in our review. Three non comparative case series reports[10-12] and one case study were excluded for level of evidence.[13] Neither of the included studies used MRI measures prospectively to make decisions on thrombolysis. Both, however, provided correlations with surrogate measures which may be useful in clinical decision making. Recanalisation and initial diffusion-weighted imaging (DWI) lesions were found to correlate with clinical outcome and infarct volume at 60 days. In addition, in patients treated with intravenous tPA, time to peak was correlated with recanalisation at day 1. Thirteen of 15 patients (93 percent) whose baseline time-to-peak was less than or equal to 36.9 milliseconds recanalized within the first day versus 5 of 15 patients (35.7 percent) whose time-to-peak was greater than 36.9 milliseconds.[9] Suarez and colleagues[8] reported a single-center cohort in which the presence of cortical infarct on MRI was used to select patients for IA treatment following IV treatment. MR imaging added 17 minutes to the treatment protocol and thus was felt to be feasible but due to the absence of a comparison group no comment can be made about marginal effectiveness over current treatment protocols.

Intervention I

Do CT perfusion/angiography affect the safety and efficacy of thrombolytic therapy for acute ischemic stroke? Three studies (four publications) examining CT perfusion/angiography for ischemic stroke were identified.[14-17] One potentially relevant trial[14,15] was published in abstract form and the authors were contacted to determine if subsequent articles were published. These were excluded following full text screening. Study design could not be determined in two publications and were excluded for level of evidence.[18,19] One single retrospective cohort study[16] and one case-control study,[17] published in 2001 and 2004, respectively, were included in our review.

The hyperdense MCA sign was evaluated in a small cohort of patients treated with either IV or IA Thrombolysis.[17] The hyperdense MCA sign was associated with a greater probability of recovery with IA than intravenous treatment (37 percent versus 13 percent). This observational data[17] suggests that this sign may be used as a tool to triage patients between intravenous and IA treatment. There is a higher probability that proximal large vessel occlusion as reflected by this sign may be associated with worse outcomes intravenously. This observation will require testing in a prospective study.

Kilpatrick and colleagues[16] reported on a retrospective cohort of 51 patients from a single center between 1997 and 2000. A CT angiogram showing patent vessels was associated with a rate of infarct of 7 percent (1/14 patients) while CT angiogram showing occlusion had an infarct rate of 60 percent (6/10) (p=0.008).

Intervention J

Are community education programs effective in reducing stroke-related disability and mortality? One controlled clinical trial,[20] six before-after studies,[21-26] and one study for which the study design could not be determined,[27] investigated the use of community education programs for acute stroke. Subsequently, seven studies were excluded for level of evidence.[21-27] Only one study[20] was included for our review. This study was a controlled clinical trial and was published in 2003.

Morgenstern et al.[20] reported on the third phase of the TLL Temple Foundation Stroke Project. Target behaviors of lay community (the "at-risk group"), EMS, ED physicians, neurologists, and community primary care providers were identified, and educational and infrastructure changes were initiated. A portion of the multilevel intervention public service announcements were created using local role models, volunteers were trained to take the message to community groups, and educational pamphlets were distributed.

Intervention K

Are designated centers effective in reducing stroke-related disability and mortality? It has been hypothesized that to increase utilization of thrombolytics, a dedicated stroke center strategy should be developed.[28] No studies meeting eligibility criteria for investigating the use of designated centers as defined by the Brain Attack Coalition were identified by our searches.[28] The studies we included were felt to most closely resemble the model of a designated stroke center as defined by the Brain Attack Coalition and detailed by Alberts et al.[28] in their recommendations for the establishment of primary stroke centers. Both studies were single prospective cohort designs and were published between 2000 and 2003.

Hill et al.[29] reported on building a "brain attack" team to administer thrombolytic therapy to patients with acute stroke and on their initial experience with IV-administered thrombolytics. A complex system of interventions involving all levels of the system involved in acute stroke care was reorganized. Over the course of the study period improvements in certain parameters were noted. Overall, symptom onset to treatment time was significantly decreased from a mean of 167.8 minutes to 147.4 minutes.[29]

Lattimore and colleagues reported on a similar process of designation and implementation of processes to enhance thrombolysis. An increase in the proportion of ischemic stroke treated with tPA from 1.5 percent to 10.5 percent was noted.[30]

Intervention L

Are ED protocols for the management of acute stroke effective in reducing disability and mortality? Our search identified one case-control study,[31] two single prospective cohort studies,[32,33] two single retrospective cohort studies,[34,35] two non-comparative case series studies,[36,37] and two studies whose design could not be determined.[38,39] The case-control and non-comparative studies were excluded for level of evidence. Four studies, published between 1999 and 2003, examining the effect of ED protocols for management of acute stroke met our eligibility criteria and were included in our final analyses.[32-35]

Smith et al.[34] reported on the establishment of ED procedures and training established for the purposes of thrombolytic treatment. The program relied on ED physicians, with neurology consultation, as primarily responsible for treatment. Treatment times in this model compared favorably with those in models involving comprehensive stroke team response. A similar effort is reported by Akins.[35] Similar treatment times were achieved when ED physicians treated as compared to consulting neurologists. The rate of protocol violations was initially higher in the ED group (30 percent versus 5 percent) than the neurologist group but was reduced by staff education. Jahnke et al.[33] described a comprehensive stroke pathway implemented in the ED. Following this intervention the stroke pathway was initiated in 97 percent of patients as opposed to 40 percent prior. The door to needle time decreased from a mean of 111 minutes to 77 minutes.

Discussion

Currently, available data do not support a role for surgery in the treatment of acute intracerebral hemorrhage. Results, however, do not preclude benefit from surgery which involves modalities other than those studied in the acute trials (e.g., minimally invasive technologies) or treatment of hemispheric hematoma at very early timeframes. Further, the available literature did not comment on cerebellar hematoma and thus this analysis does not apply to infratentorial hemorrhage.

In spite of potential importance, availability of therapy and ease of administration of antihypertensive agents, very little data exists to suggest that their use is of benefit (or results in harm) in the setting of acute ICH. A similar situation exists regarding glucose management for acute ischemic stroke. Further studies are required in both these areas.

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artery distribution. The evidence for this intervention, however, remains less robust than for IV therapy. Limited data is available regarding patient characteristics predicting outcome. The system changes required to ensure prompt delivery of appropriate therapy are complex and operate on multiple levels. In spite of their critical role, little data exists regarding the efficacy of these interventions and, in particular, the relative efficacy of various components with regard to patient outcomes.

Ultrasound for enhancement of thrombolysis in the setting of MCA occlusion has suggested efficacy in two studies and a definitive trial to demonstrate the benefit and risks is required.

CT and MR imaging for patient selection and prediction of outcome in thrombolysis has yet to be prospectively evaluated. The two included CT studies[6,7] differ in onset to evaluation time with only a weak correlation between CT changes and outcome seen in the trial enrolling patients from 0-6 hours. Neither study quantified CT changes. The Alberta Stroke Program Early CT Score (ASPECTS) score is an easily quantifiable scoring system for early infarct changes.[40] Retrospective evaluation of the ASPECTS score suggests that values below 7 correlate with poorer outcomes. As CT is widely available, this system deserves further exploration. Additional information relevant to treatment decisions may be provided by CT angiography. Occlusion of proximal vessels is associated with higher rates of infarction and thus may influence treatment modalities.

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Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Ottawa Evidence-based Practice Center, under Contract No. 290-02-0021. It is expected to be available in July 2005. At that time printed copies may be obtained free of charge from the AHRQ Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 127, *Acute Stroke: Evaluation and Treatment.* In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

Chapter 1. Introduction

Overview

Stroke defines an acute vascular event in the brain and is a leading cause of death and disability. The next two decades are expected to see an increase in the burden of this disease worldwide, due to an increase in absolute numbers and proportions of populations in older age groups. Ischemic stroke is the most common type of stroke and is the consequence of decreased blood flow to a portion of the brain; hemorrhagic stroke, on the other hand, is the result of bleeding into the brain. Thrombolytic therapy, most commonly with tissue plasminogen activator (tPA), attempts to remove the obstruction to flow. Administration of the thrombolytic agent results in the dissolution of blood clots and re-establishment of the supply of oxygen and nutrients to the affected area prior to irreversible ultra-structural changes heralding cell death. While it is the only available therapy for acute ischemic stroke, wide application has been primarily limited due to the narrow time constraints imposed by the natural history of cerebral ischemia, which results in irreversible changes within hours.

Effective deployment of time dependant therapies is contingent upon symptom recognition. Community interventions, consisting of public education campaigns, have been promoted and deployed as a means to increase utilization of thrombolysis for acute ischemic stroke by increasing the number of patients presenting within the time window for treatment. The term "brain attack" has been promoted as a means to emphasize the urgency of seeking early treatment. Myocardial ischemia shares similar risk factors and treatment benefits linked to a time dependent intervention. Previous experience with community interventions of this type in acute myocardial infarction, which target thrombolysis to cardiac ischemia, have shown mixed results and the potential impact of similar campaigns on acute stroke outcomes, is unclear. Other system changes include designation of acute stroke centres and alterations in emergency department (ED) protocols.

Evidence is emerging that patient selection by time of stroke onset, imaging characteristics, intraarterial (IA) treatment delivery of thrombolytic agents, and use of intercranial thrombus disruption, may increase the efficacy of thrombolytics. Normalization of serum glucose, acute blood pressure management, and surgical evacuation of intracerebral clot, may be of added benefit in some circumstances. At this time, a review of the impact of these interventions on clinical stroke outcomes is warranted in order to assist with their implementation.

Objectives

The purpose of this report is to systematically review the available literature in the field of acute stroke evaluation and treatment, in order to provide organized evidence relating to a number of objectives put forth by the AHRQ. The findings of the report are intended to assist the American Association of Health Plans (AAHP) and its member health plans in their development and translation of the research findings into practical information for healthcare providers and consumers, where applicable. The University of Ottawa Evidence-based Practice Center (UO-EPC) task involves the following three objectives:

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/acstroketp.htm

(1) To determine what interventions for acute stroke (delivered within the first 24 hours from onset of symptoms) are effective in reducing stroke-related morbidity or mortality. (Note: some studies that initiated interventions beyond 24 hours were also included if they were deemed relevant to the topic area being studied). As this question was very broad it was refined into 12 key questions.

(2) To review how the safety and effectiveness of these interventions vary with the timing of intervention in relation to onset of symptoms.

(3) To determine what is the evidence that specific systems of care (i.e., dedicated stroke programs) improve outcomes of acute stroke.

Background

Stroke has been defined as "rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than of vascular origin."[1] Mechanistically, stroke may be organized into ischemic and hemorrhagic forms. In ischemic stroke the primary pathology is one of occlusion of arteries carrying blood to the brain. Hemorrhagic stroke includes intracerebral hemorrhage (ICH), which is the consequence of vessel rupture and cerebral damage due to pressure and toxic effects of blood within the closed space of the skull, and sub-arachnoid hemorrhage (SAH), which is bleeding into the space outside the brain but within the subarachnoid membrane. While SAH is often included in the definition of stroke for the purposes of surveillance and descriptive epidemiology, its presentation and management are sufficiently unique that it will not be considered for this analysis.[2]

The incidence of stroke is strongly age-linked.[3] The increasing median age of national populations occurring worldwide has led the World Health Organization (WHO) to target this disease for surveillance with the goal of reducing associated morbidity and mortality.[4] In developed countries such as the U.S., the burden of disease is expected to be higher due to the age structure of these populations and has led to the call for the development of organized systems of stroke care, with particular emphasis on thrombolytic therapy.[5] Public education, which teaches the symptoms of acute stroke and emphasizes the need to seek urgent care, has been seen as a means of increasing acute stroke treatment rates and, therefore, improving outcomes.[6]

Stroke Epidemiology

Cerebrovascular disease is the third leading cause of death on a global basis, with rates for males ranging from 340.3 cases per 100,000 population in the Russian Federation to 58.7 cases per 100,000 in the U.S.[7] An estimated 700,000 strokes occurred in the U.S. in 2002, with approximately 500,000 cases being first events,[7,8] with mortality rates ranging from 39 cases per 100,000 in New York State to 80.8 per 100,000 in South Carolina. The global burden of mortality was estimated at 4.7 million in 1995.[9]

Mortality rates due to stroke have declined for a number of populations in the twentieth century.[10-13] In the U.S., the rate of decline was approximately 0.5% per year between 1900 and 1920, and approximately 1.5% per year from 1950 to1970.[14,15] All age groups were affected, suggesting that this was a period effect rather than a cohort effect. Interestingly, this decrease began long before effective therapies for stroke prevention treatment were available, and thus cannot be ascribed to medical care. This trend has not continued in the latter part of the century. In Rochester Minnesota, the incidence of stroke stabilized at approximately 150 per 100,000 population and remained so from the mid-1970's to the mid-1990's.[16,17] While the initial period of this stabilization coincided with the introduction of CT scanners, and thus, may be explained by an increased probability of diagnosis, such an effect is less likely to explain a persistent stabilization through the next two decades.

While most states have shown a decrease in the mortality rate due to stroke between 1990 and 2000, Alaska, Maryland and Oregon have shown increases over this time period. Between 1979 and 2001, stroke discharges from short stay hospitals in the U.S. increased by 25%.[7]

Stroke incidence in males is 1.25 times greater than that for women. Age-adjusted stroke incidence rates per 100,000 population are 167 for White males, 138 for White females, 323 for Black males, and 260 for Black females.[18] The risk for Black Americans is greater than that for White Americans with a risk ratio of 5 for the 35 to 44 year age group in the greater Cincinnati/northern Kentucky study.[19,20] The risk ratio is greater than 1 for all age groups, although it approaches unity in the over 85 age group. It is unclear if this risk ratio reflects biologic or social factors or some combination thereof. In spite of the increased risks, fewer blacks in the U.S. are candidates for thrombolytic therapy.[21]

Hispanic Americans may have an age-specific stroke incidence that differs from non-Hispanic whites. Stroke surveillance in this population is challenging and the databases are limited. The National Longitudinal Mortality Study (NLMS) suggests that for the 45 to 59 year age strata, the relative risk for Hispanic men and women is 1.0 and 1.17, respectively. For the 60 to 74 year strata, it is 0.53 to 0.76.[22] These figures should be interpreted with caution due to small numbers. It is unclear if the reduced incidence in the older age strata reflects a true effect or incomplete ascertainment.

A link between incidence, outcome, and socioeconomic status has also been documented in the U.K., where unskilled manual workers have a 60% higher risk of stroke than professionals, along with a 50% higher age-adjusted mortality rate.[23]

While age-specific death rates for stroke have fallen over the last century,[24-26] the number of such deaths is currently, and is expected to remain, greater for women than men.[9] The projected increase in absolute numbers in the U.S. is from approximately 700,000 in 2002 to 1,136,000 in 2025.[8]

Both the pending increase in stroke mortality and the gender differences may be explained by the strong relationship between stroke and age. It has been over 30 years since the logarithmic relationship between stroke mortality and age was described by Kurtzke.[27,28] Consequently, it is expected that the burden of disease will increase in absolute terms due to the increase in population median age and the alteration of the population age structure, despite stable or falling age-adjusted incidence rates.

The risk factors for stroke overlap significantly with those for ischemic heart disease. After age, the most important risk factor is blood pressure. The risk of stroke increases across the measured pressures for both systolic and diastolic pressure.[29] For each 10 mm Hg increase in systolic blood pressure or 5 mm Hg increase in diastolic pressure, the relative risk of stroke increases by a factor of 2.3.[30] Anti-hypertensive treatments result in significant reductions of risk for first and subsequent stroke.[31-33,33,33,33,34] Diabetes and smoking each increase the relative risk by a factor of 2.[35-39] Hyper-homocysteinemia is an emerging risk factor with a relative risk of 5 to 7 between the highest and lowest quartiles of serum homocysteine concentration.[40] Atrial fibrillation likewise carries a relative risk of 5 for stroke. The link to serum cholesterol is somewhat more complex for stroke than for coronary artery disease. Observational studies do not show an increased risk with elevated cholesterol levels.[41] Low cholesterol may result in an increased risk of hemorrhagic stroke.[41] In spite of this, a major therapeutic trial of lipid lowering therapy has demonstrated a reduction in ischemic stroke incidence without an increase in hemorrhagic stroke.[42] However, in a sub-group within this trial, patients with prior ischemic stroke randomized to statin therapy did not show a reduced incidence of stroke; the benefit among this cohort was in reducing subsequent coronary artery disease.(HPS analysis, LANCET)

Stroke Costs

Stroke currently consumes significant resources through healthcare costs and disability. Twenty-eight percent of total stroke incidence occurs in individuals under the age of 65,[43] and accounts for 20% of all acute care beds, and 25% of all chronic care beds.[44] The acute cost per stroke in Ontario was estimated at C$27,500 in 1996. The absolute number of hospitalizations for stroke has been increasing for the past 20 years with a projected increase in hospitalizations of 10% to 15% between 1996 and 2016.[9] Hospitalization makes up 87% of the total direct cost of stroke care, which was estimated by the Heart and Stroke Foundation of Canada to be 2.8 billion dollars in 1996.[9] However, this cost does not include costs related to either short- or long-term disability. Such costs may be considerable since, in the case of ischemic stroke, only 25% of people make a full recovery.[45] More recent costs are available for the U.S., where the estimated direct cost for stroke in 2004 is 33 billion dollars—41% of this is due to hospital costs reflecting the expense of acute care. Indirect costs due to loss of productivity are estimated at 53.6 billion dollars.[7]

Given the trends observed in stroke over the last three decades and the associated costs, stroke is, and will remain for the foreseeable future, a significant problem for North American and other societies.

Integration of Thrombolytic Therapy into Current Practice

Thrombolysis for acute stroke has received widespread, though not universal, support. It is a complex intervention making intensive use of resources and personnel, with a narrow therapeutic window. Current clinical protocols limit use to a 3-hour window from symptom onset. The Brain Attack Coalition (BAC) in the U.S. and the Heart and Stroke Foundation of Canada(HSFC) advocate for multilevel system changes to increase the number of patients

eligible for, and receiving, thrombolytic therapy.[46,47] Such advocacy has influenced public policy.

The province of Ontario, Canada is in the process of a major system change in stroke care. This process is unique among large jurisdictions and forms an important framework for initiating and evaluating such strategies. In May 1997, the HSFO of Ontario, a nonprofit group, proposed the creation of a coordinated system of stroke care for the province of Ontario. In 1998, a pilot program for regional coordination of care was launched at four sites. This was shared by the HSFO, and a joint stroke strategy-working group was established in partnership with the Ontario Ministry of Health.[48] In 2000, based on the results of the initial experience, the Ministry of Health funded a coordinated province-wide stroke strategy. Over the next 3 years, a total of nine regional stroke centers were designated. The development of integrated acute stroke care was seen as a key role of these centers.

The process of delivering acute stroke therapy involves a pre-hospital phase and an ED phase. The latter requires a rapid, intense, and at times, parallel application of clinical, radiological, and biochemical analysis of the potential candidate. These evaluations serve to interpret compliance with eligibility criteria, thereby maximizing the probability of outcomes that parallel results published by the National Institutes of Neurological Disorders and Stroke (NINDS) .[49] The main determinant of eligibility is time since onset.[50,51] Further, within the eligible group, regression analysis suggests that earlier treatment is associated with better outcome.[51] Attention has, therefore, been focused on the pre-hospital phase. Shortening delay time in this phase requires recognition of symptoms, a decision to seek care, and transportation to a facility capable of delivering care. Multiple mass media strategies were evaluated by the HSFO.[52] A positive effect was noted in the ability to name two or more warning signs of stroke after the mass media campaign and, therefore, a subsequent television campaign was launched in Ontario in October 2003. It is not clear, however, that such an education strategy increases the number of potentially treatable patients or that it improves outcomes. Furthermore, such an intervention runs a risk of increased number of non-stroke patients presenting to the ED. Evaluation and treatment of such patients might be expected to increase resource utilization and possibly worsen outcomes by exposing individuals to the risk of treatment who do not have any possibility of benefit.

Patient Selection for Thrombolysis

Current treatment protocols for thrombolysis rely on the entry criteria used for the NINDS Trial.[49] The NINDS trial published in 1995 was the pivotal evidence leading to regulatory approval of tPA in North America.[49] Clinical protocols currently used for thrombolysis use trial criteria regarding patient selection and blood pressure management. This trial has received much attention and has been reanalyzed independently on at least two separate occasions.[53,54]

NINDS criteria require a diagnosis of acute ischemic stroke of less than 3 hours' duration, absence of hemorrhage on CT scan, good blood pressure control, a NIH Stroke Scale Score of greater than 4 along with exclusion of those at high risk for bleeding with therapy. Reanalysis of the results from the original trial suggest a better outcome if treated within 0 to 90 minutes compared to 91 to 180 minutes.[55] The stringent time constraints decrease the absolute number

and percentage of individuals receiving treatment. This review will investigate the data regarding the relationship between onset to treatment time and outcome.

The Cerebral Ischemic Penumbra denotes that a portion of the brain which has been rendered inoperative by ischemia but has not yet died.[56] Time since onset forms a surrogate for tissue viability.[57] Imaging of acute stroke holds the possibility of identifying the ischemic penumbra on a physiologic basis and thus increasing safety, efficacy, and through an extension of the time window applicability of revascularization therapy. We will review the evidence that pretreatment imaging improves stroke outcomes.

Community Education Programs for Stroke

The rates of treatment of acute stroke with the thrombolytic, tPA, are low—2% in the U.S.[58] and 1.4% in Canada.[59] The narrow eligibility criteria, the lack of comfort with acute neurology by many physicians and the perception of a high risk of adverse events contribute to the low treatment rates.[50] The most significant limiting criterion is time since onset of symptoms. Englestein and colleagues retrospectively examined the records of patients admitted to a New York hospital with a diagnosis of stroke, for the presence of exclusion criteria for tPA.[60] Of 201 patients identified by ICD-9 codes, 94% were excluded based solely on time of presentation to the ED.[60] Reports from other centers have documented rates of exclusion by delay time criteria of 44%,[61] with speculation that differences arise due to variations in public awareness of symptoms in different communities.[60] In Calgary, 1,168 patients with ischemic stroke were prospectively identified and evaluated for reasons for exclusion for tPA therapy. Of these, 73.1% presented beyond 3 hours after symptom onset and thus could not be considered for treatment.[51] This was the most common reason for exclusion from treatment. An education effort leading to better awareness of symptoms may, therefore, improve treatment rates.

The Chain of Recovery Writing Group has identified a sequence of events that must take place in order to access time-dependent therapies in emergency situations.[62] By analogy with processes successfully deployed for acute myocardial infarction and trauma, the chain consists of: identification of symptoms by patient or bystander; activation of the EMS; alerting treating center; and, diagnosis and treatment.

Initiation of this entire sequence of events is contingent upon the correct identification of symptoms along with the appreciation of their gravity. In contrast to major trauma, the seriousness of stroke symptoms may not be obvious.[62]

Gaps have been identified in the public knowledge of stroke symptoms. A population-based random-digit telephone survey was conducted in the Cincinnati region.[63] While 70% of 2,173 respondents correctly identified at least one symptom of stroke, groups at highest risk of stroke, including people over 75 years of age, men, and blacks, were the least knowledgeable. In a national U.S. phone survey of 750 adults over age 50, 42% could not identify limb numbness or weakness as stroke symptoms.[6] Forty percent of respondents were unaware that stroke occurs in the brain. Of patients with stroke, 39% were unable to identify any symptoms of stroke. This proportion was worst for those over the age of 65 than for those under 65 (47% vs. 28%, p=0.016).

Williams interviewed consecutive admitted stroke patients within 72 hours of stroke onset regarding knowledge of, and attitude to, stroke symptoms.[64] While 38% of 67 individuals purported to know stroke symptoms, only 25% correctly interpreted their symptoms as being due to stroke. Eighty-six per cent of those arriving after 3 hours felt that the symptoms were not serious. Interestingly, patients with prior stroke (46% vs. 16% p=0.03) were more likely to ascribe their symptoms to stroke but were no likelier to seek early attention (19% vs. 39% p=0.35). Ambulance transport was independently associated with early arrival (OR 5.55, 95% CI 1.37 to 22.6). Instructions to use an ambulance in the setting of acute stroke may, therefore, result in earlier intervention and improved outcomes.

Wein reported on the individual activating the EMS in 429 validated admitted stroke patients, as part of the TLL Temple Foundation Stroke Project.[65] Of these, 38% (163) of patients arrived by ambulance. In these cases, the person activating the system was: self, 4.3%; family member, 60.1%; paid caregiver, 18.4%; and, coworker or other, 12.9%. It was concluded that educational efforts directed exclusively at patients themselves were likely to be of low yield and wider educational efforts were required.

Consequently, a number of calls have been made for public education to increase knowledge of stroke symptoms.[6,66-68] Such community interventions are expected to decrease delay time and consequently improve the thrombolysis treatment rates. However, several concerns about this approach remain. First, the experience in acute myocardial infarction raises concern about the effectiveness of media campaigns for public education in a similar disease state.[69] Second, knowledge may not translate into action. Patients involved in the Asymptomatic Carotid Atherosclerosis Study[70] received targeted education on the warning signs of stroke. In spite of these efforts in a group motivated enough to participate in the study, only 40% of all first events were reported within 3 days of occurrence.[70] Participants in an advertised stroke-screening program were assessed before and after completion of a detailed evaluation of individual risk factors and counseling on risk factors and symptoms.[71] After 3 months, 77% of participants could name warning signs, compared with 59% prior to the intervention; however, 73% reported no change in lifestyle in spite of an individualized written plan of action provided at the screening. Finally, the symptoms transmitted to the public in education campaigns are non-specific.[52] Proper identification and immediate action by the public may, therefore, result in an increase in the number of non-stroke patients reporting to the ED and thus have no impact on outcomes.

At this stage, while community education programs appear to be attractive, it is clear that further review of their effectiveness is warranted.

Acute Stroke Centers

Community education programs do not occur in isolation. It is clear that the activities carried out at the receiving ED may have a significant impact on treatment rates and subsequent outcomes. The initial experience in the Cincinnati program suggested rates of hemorrhage with thrombolysis as high as 16% associated with an almost 50% rate of violation of protocols.[72] This experience was followed by a Stroke Quality Improvement Program in nine hospitals and a subsequent report from the same group suggested the effectiveness of this intervention, reporting a protocol deviation rate of 19% with symptomatic intracranial hemorrhage rate of 6.4%, a

subsequent reduction over the previously reported adverse event rate.[73] The Brain Attack Coalition has suggested criteria for the designation of stroke centers.[5] Key elements of stroke centers include acute stroke teams, stroke units, written care protocols and an integrated emergency response system. Support services felt to be important include the availability and interpretation of CT scans and rapid laboratory testing. The criteria for such centers were developed on the basis of a literature review of English language articles published between 1966 and 2000, with recommendations issued after review by an expert panel. Establishment of stroke centers of this type has been promoted within North America. An estimate of their effectiveness would be helpful in terms of planning and justification of resource allocation in the wider context of healthcare. Thus, it is our objective to systematically review literature pertaining to the use of designated stroke centers to determine their effectiveness in the for acute stroke treatment.

Summary

Stroke is common, lethal, debilitating, and costly. Treatment in the acute phase is effective, although available to only a small number of individuals with stroke, resource intensive, and potentially hazardous. Increasing the probability of treatment is beneficial on the individual level and is expected to also be beneficial at the societal level. The number of potential candidates accessing acute stroke treatment is significantly limited by the narrow time window between the onset of symptoms and the initiation of treatment. It is widely believed that strategies to increase public awareness of stroke and EMS diagnosis are likely to increase the number and proportion of patients who are able to receive effective but time-dependent interventions. Prior to advocating wide implementation of pre-hospital programs in a complex system, it is important to evaluate the likelihood of success of these strategies within plausible variations of the effects of these strategies and the risks and benefits of thrombolytic treatment of acute stroke.

Chapter 2. Methods

Overview

The UO-EPC's evidence report on acute stroke is based on a systematic review of the scientific-medical literature to identify, and synthesize the results from studies addressing the 12 questions elaborated by the Acute Stroke Review Panel. Together with content experts, UO-EPC staff identified specific issues integral to the review. A Technical Expert Panel (TEP) provided expert guidance as to the conduct of the systematic review. Evidence tables presenting the key study characteristics and results from each included study were developed. Summary tables were derived from the synthesis tables. The methodological quality of the included studies was appraised, and individual study results were summarized. For some objectives, where meta-analysis was not appropriate, a narrative interpretation of the literature alone was provided.

Key Questions Addressed in This Report

From the UO-EPC Task three primary objectives, the following key questions were derived and addressed in this report.

Intracerebral hemorrhage (ICH)

- Does surgery for adults with acute ICH reduce stroke-related mortality and disability? **(Intervention A)**
- Does antihypertensive treatment reduce stroke-related mortality and disability? **(Intervention B)**

Cerebral Infarction

- Does intraarterial (IA) thrombolysis reduce stroke-related mortality and disability in adults with acute ischemic stroke? **(Intervention C)**
- Does treatment to normalize blood glucose levels reduce stroke-related mortality and disability in adults with acute stroke? **(Intervention D)**
- Does mechanical thrombus disruption reduce stroke-related mortality and disability in adults with acute ischemic stroke? **(Intervention E)**

Patient selection for thrombolysis

- Is the effectiveness and safety of thrombolytic therapy for adults with acute ischemic stroke affected by time from onset to treatment? **(Intervention F)**
- Do pretreatment CT scoring systems affect the safety and efficacy of thrombolytic therapy for acute ischemic stroke? **(Intervention G)**
- Do pretreatment MRI scoring systems affect the safety and efficacy of thrombolytic therapy for acute ischemic stroke? **(Intervention H)**

- Do CT perfusion/angiography affect the safety and efficacy of thrombolytic therapy for acute ischemic stroke? **(Intervention I)**
- Do patient characteristics (i.e., age, gender, co-morbidities, functional status, medications) alter the safety and effectiveness of thrombolysis for acute ischemic stroke? When available, this data was extracted from the studies and is reported under the individual interventions.

Systems of care

- Are community education programs effective in reducing stroke-related disability and mortality? **(Intervention J)**
- Are designated centers effective in reducing stroke-related disability and mortality? **(Intervention K)**
- Are ED protocols for the management of acute stroke effective in reducing disability and mortality? **(Intervention L)**

We did not systematically review the effectiveness of IV-tPA. This has been adequately assessed in existing reviews and has been well established for patients presenting within 3 hours. The seminal trial and a previously published meta-analysis is presented in the discussion section.

Analytic Framework

The purpose of this report was to systematically review the available literature in the field of acute stroke evaluation and treatment, in order to determine which interventions (delivered within the first 24 hours from onset of symptoms) are effective in reducing stroke-related morbidity or mortality. We also investigated the relationship between the safety and effectiveness of thrombolytic therapy and how they varied with the timing of the intervention in relation to the onset of symptoms. Effective acute stroke therapies require a system for rapid delivery of complex interventions and as such, occur within the context of an EMS capable of identifying and treating appropriate individuals. Each component of this system is in itself an intervention, which may result in harm if inappropriate candidates are submitted to treatment while others are missed. Thus, we have reviewed the evidence that specific systems of care (e.g., dedicated stroke programs) improve outcomes for patients with acute stroke.

The analytic framework is presented in Figure 1. This framework illustrates the review's context and our conceptual approach regarding relationships between symptom onset, interventions/decisions, and outcomes within the context of acute stroke. Within the framework, arrows indicate linkages (either preventive or treatment) with associated questions investigated by our review. For example, when an individual develops symptoms, what is the evidence for the effectiveness of community education programs in influencing the individual's decision to seek emergency medical attention. The framework also highlights our primary outcome measures associated with these linkages used to define either success or failure of these interventions (i.e., patients are well, disabled, or dead).

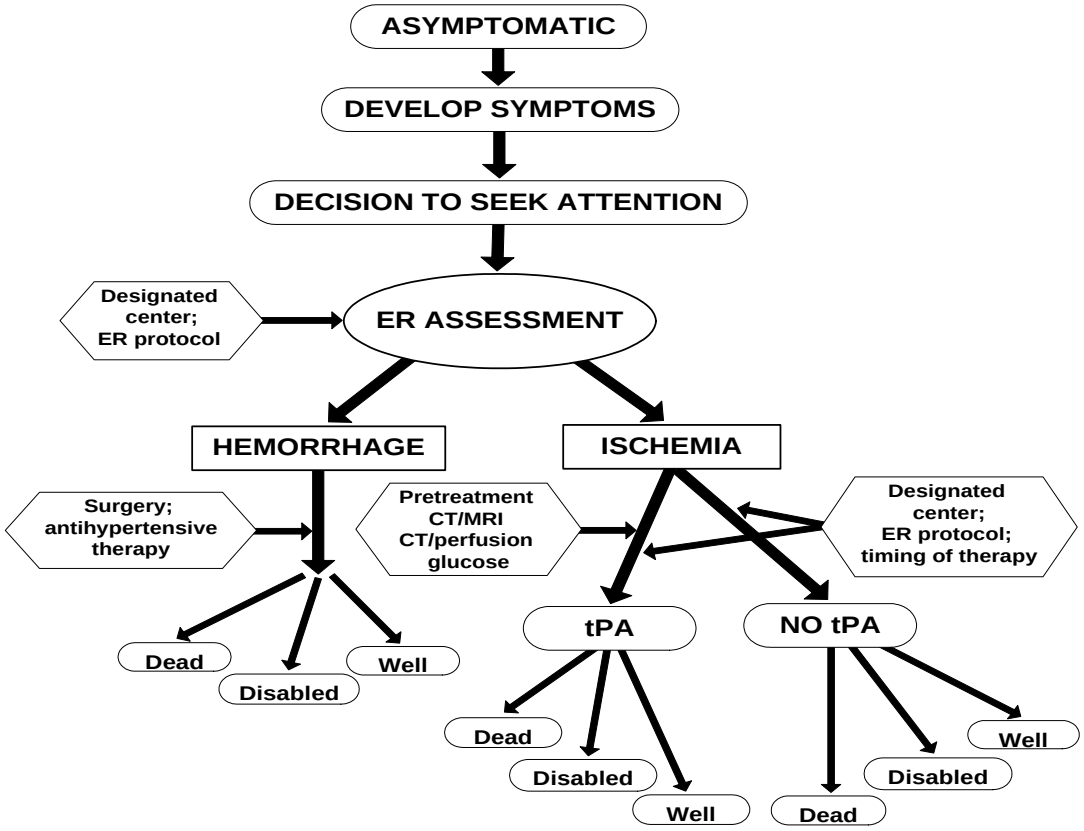

Figure 1. Analytic Framework for evaluation and treatment of acute stroke. Populations of interest in rectangles. Exposure in oval. Outcomes in rounded rectangles. Effect modifiers in hexagons. Solid connecting arrows indicate associations and effects reviewed in this report.

Study Identification

Search Strategy

Comprehensive search strategies for each individual question were developed and tested in the Medline database (Search Strategy 1 in Appendix A). Initially, existing searches from the Cochrane Stroke Group were consulted. Indexing terms from relevant articles identified in Medline were used, and terms and limits were applied (such as age and trial type). These were repeatedly tested to ascertain recall and precision. These strategies were modified in consultation with the review team and then executed by two librarians, one who built the search and another who validated the strategies. Many of the searches were limited to adult age groups and randomized controlled trials (RCTs) using the Highly Sensitive Search Strategy (HSSS), designed by the Cochrane Collaboration to identify RCTs in Medline. All searches related to question 1 were limited by age and study design, as were all question 2 topics except for question 2d, which was limited to adults but was not limited by the HSSS. Searches related to question three where not limited by either study design or age. Language restrictions were not imposed. Non-English articles were included but not used.

The databases searched were Medline (1966 to April Week 4 2004), Embase (last 6 months) and CINAHL (1982 to April Week 5 2004) using the OVID interface. Also searched were the Stroke Trials Directory and the Cochrane Stroke Group Registry, as well as conference proceedings from the 28th International Stroke Conference 2003 (*Stroke*, Feb 2004) and the American Academy of Neurology Annual Meeting (published in *Neurology*). The Effective Practices and Organisation of Care (EPOC) registry was searched by the Cochrane review group for controlled studies, including controlled before and after (CBA) and interrupted time series (ITB) designs.

Records identified through electronic searching were downloaded, and duplicate records identified and removed using citation management software (Reference Manager®). A total of 7,320 unique records were retrieved on the initial running of the search. An additional 163 unique records were retrieved on the updated search run nearing the project's completion. Therefore, after bibliographic records were retrieved through database searches and duplicate records were removed; a total of 7,483 unique items remained. The review team nominated four additional records. At the suggestion of the TEP, four prominent principle investigators were contacted regarding potential data from trials that had been prematurely terminated. Two investigators responded, however no unpublished data was provided.

Eligibility Criteria

Published and unpublished studies, reported in English,[74-76] involving any research design (e.g., RCTs reported in English) and enrolling both male and female adult participants (age >16 years), including members of racial/ethnic populations with acute stroke, were eligible for inclusion if each also met the criteria outlined in Table 1. For studies regarding systems of care

for acute stroke, the intervention studied may not be applied to patients with acute stroke (i.e., community education programs to increase awareness of symptoms of stroke) but they must be applied to improve the care of patients with acute stroke.

Table 1: Inclusion criteria

Parameter	Acute Stroke	Systems of Care
Design	Does the article discuss an intervention occurring within 24 hours of stroke?	Does the article report an original intervention trial or series with goal to improve the care of patients with acute stroke?
Intervention	**Intracerebral hemorrhage (ICH):** surgery or antihypertensive treatment **Ischemic Stroke** Intraarterial thrombolysis, normalization of blood glucose, mechanical thrombus disruption, timing of intravenous (IV) thrombolytic therapy, utilization of pretreatment CT, MRI or CT perfusion/angiography scoring systems prior to IV thrombolytic therapy	Community education programs, designated stroke centers, ED protocols for the management of acute stroke
Outcome	Reduction in related morbidity and mortality of stroke	Reduction in related morbidity and mortality of stroke. Improvement in processes of care

Study Selection Process

The results of literature searches were posted to the UO-EPC's internet-based software system for review. To enhance the speed and efficiency of conducting and managing the systematic review process, this software, which resides on a secure website, was used to enable the electronic capture and internal comparison (relative to explicit criteria) of multiple reviewers' responses to relevance screening questions, and to requests to abstract specific data (e.g., study quality) from bibliographic records or full reports.

All results of searches for evidence were provided to two reviewers for assessment. A 3-step process was used. First, all studies were screened by both reviewers by reviewing the bibliographic record (i.e., title, authors, key words, abstract) and applying the inclusion/exclusion

criteria. The record was retained if it appeared to contain pertinent study information according to the inclusion/exclusion criteria or if there was not enough information provided to determine eligibility at this level. If the reviewers did not agree in finding at least one unequivocal reason for excluding the study, it was entered into the next phase of the review. The reasons for exclusion were noted using a modified QUOROM format (Appendix D).[77]

The second step of the review required screening of the full report of the study. The full reports were not masked given the equivocal evidence regarding the benefits of this practice.[78-80] To be considered relevant at this second level of screening, all eligibility criteria had to be met as determined by both reviewers.

There are various templates for grading the strength of evidence. Almost all of these approaches rate randomized controlled trials (RCTs) at the top of the ranking scheme. This is not surprising as RCTs have a comparator group and participants are assigned to all treatment groups through randomization. Randomization is unique in that it 'controls' for known confounders and, perhaps more importantly, unknown ones. Adequate randomization has been shown to reduce the influence of bias on the results of RCTs. Other designs, such as cohort studies and case control ones, also offer some control over the influence of bias. This is because such designs incorporate a comparator group, even though there is no randomization.

What is less clear is the extent of bias in studies for which there is no controls (i.e., comparator group). Although it is feasible to provide data analytical "solutions" to such designs there is no adequate way to assess the influence of bias. In such circumstances it is pragmatic and scientifically prudent to limit systematic reviews to primary studies that have a comparator group.

Thus, in situations where multiple levels of evidence are available, it is generally preferable to focus available resources on synthesis of studies that provide higher levels of evidence (e.g. RCT, CCT, etc.). In addition to limiting bias, such studies focus on the contrast between groups, the impact of differences between studies may be much less than is often the case with studies lacking control groups. Thus, restricting our primary attention to higher levels of evidence, RCTs, CCT, cohort and case-control studies was thought to help limit one of the most troublesome issues in meta-analysis, namely statistical heterogeneity.

As such, and with approval from the TEP, a third level screening was implemented beyond full relevance assessment where we sought to include only, whenever possible, reports of RCTs. For questions for which there were at least three RCT reports, designs of other reports were excluded. Where reports of RCTs did not exist, lower level evidence was included, such as reports of observational studies.

All disagreements were resolved by consensus and, if necessary, a third party facilitated. Excluded studies were noted as to the reason for their ineligibility (see List of Excluded Studies for Level of Evidence and List of at the end of the report).

Data Abstraction

After training and following a calibration exercise involving two studies, two reviewers independently abstracted the contents of each included study using an electronic Data

Abstraction form developed especially for this review (Appendix C). Once a reviewer completed their work, they then checked all of the data abstracted by their counterpart. Data abstracted included the characteristics of the:

- Report (e.g., publication status, year of publication)
- Study (e.g., sample size; research design; number of arms)
- Population (e.g., baseline characteristics)
- Intervention (e.g., IV thrombolytics according to time delivered post stroke)
- Withdrawals and dropouts

Summarizing the Evidence

Overview

Evidence tables in the Appendices offer a detailed description of the included studies (e.g., study design, population characteristics, intervention[s] and outcome[s]), with a study being represented only once. The tables are organized by research question and study design, with designs purporting to induce less bias coming before those designs were bias might be a more substantial problem (e.g., RCTs before single group pre-post studies). Question-specific Summary Tables embedded in the text report each study in an abbreviated fashion, highlighting some key characteristics, such as comparators and sample size. This allows readers to compare all studies addressing a given question. A study can appear in more than one Summary Table given that it can address more than one research question.

Study Quality

Evidence reports include studies of variable methodological quality. Differences in quality across, and within, study designs may indicate that the results of some studies are more biased (i.e., systematic error) than others. Systematic reviewers need to take this information into consideration to reduce or avoid bias whenever possible. In this report, study quality was assessed through examination of each individual report. No attempt was made to contact the authors of any report. Quality was defined as the confidence that the study's design, conduct, analysis, and presentation, has minimized or avoided biases in any comparisons.[81] Several approaches exist to assess quality including components, checklists, and scales. For this report, we have elected to use a combination of methods in an effort to ascertain a measure of reported quality across different study designs.

For RCTs, the Jadad scale was used (Appendix C). This validated scale includes three items that assess the methods used to generate random assignments, double blinding, and a description of dropouts and withdrawals by intervention group.[82] The scoring ranges from 1 to 5, with higher scores indicating higher quality. In addition, allocation concealment was assessed as adequate, inadequate or unclear (Appendix C).[83] An *a priori* threshold scheme was used for

sensitivity analysis—a Jadad total score of ≤2 indicates low quality and scores >2 indicates higher quality. For allocation concealment, adequate = 1, inadequate = 2, and unclear = 3.

Cohort and case-control study reports were assessed using the Newcastle-Ottawa scale (NOS). The NOS is an ongoing collaboration between the Universities of Newcastle, Australia and Ottawa, Canada to develop an instrument providing an easy and convenient tool for quality assessment of nonrandomised studies to be used in a systematic review. The scale uses a "star system" in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and, the ascertainment of either the exposure for case-control studies, or the outcome of interest for cohort studies. The inter- and intra-rater reliability of the NOS have been established. The face content validity of the NOS has been reviewed based on a critical review of the items by several experts in the field who evaluated its clarity and completeness for the specific task of assessing the quality of studies to be used in a meta-analysis. Further, its criterion validity has been established with comparisons to more comprehensive, but cumbersome, scales. An assessment plan is being formulated for evaluating its construct validity with consideration of the theoretical relationship of the NOS to external criteria and the internal structure of the NOS components.[84]

We did not conduct any sensitivity analysis of quality assessments on the observational studies, since there is little by way of guidance to suggest what a poor quality study's score would be based on for these assessment instruments.

Qualitative Data Synthesis

A qualitative synthesis was completed for all studies included in the Evidence Report. A description is provided of the progress of each citation through the review process, and includes information pertaining to each report, such as their sample size. The qualitative synthesis was performed on a question-specific basis, with studies grouped according to research design (e.g., RCTs, observational studies). Each synthesis includes a narrative summary of the key defining features of the study report, if stated, (e.g., *a priori* description of inclusion/exclusion criteria), population (e.g., diagnosis-related), intervention/exposure (e.g., use of IA thrombolysis), outcomes, study quality, applicability, and individual study results. A brief study-by-study overview typically precedes a qualitative synthesis.

Quantitative Data Synthesis

We performed meta-analyses of RCTs when interventions were clinically homogenous and two or more studies reported an outcome of interest. We focused on two dichotomous outcomes: (1) death, and (2) death or disability, measured as scores of 0 or 1 on the modified Rankin Scale (mRS). Odds ratios comparing the outcomes in the experimental and control groups were used as the effect measure for pooling. The chi-square test and the associated I^2 statistic[85] were used to assess heterogeneity in odds ratios. Meta-analytic pooling was performed using the DerSimonian and Laird random effects method.[86]

Chapter 3. Results

Results of Literature Search

A total of 9,994 bibliographic records were retrieved through database searches (QUOROM flow chart, Appendix D). After 2,511 duplicate records were removed, 7,483 unique items remained. The reviewers nominated an additional four potentially relevant studies. A total of 7,487 reports were evaluated against the eligibility criteria and after the initial screening for relevance, 6,098 records were excluded. The remaining 1389 reports were then retrieved and subjected to a more detailed relevance assessment. After further relevance assessment, 1,253 of the 1,389 reports failed to meet the inclusion criteria. An additional eligibility criterion of level of evidence was then applied to the 136 remaining studies. One hundred bibliographic records that were examined and categorized to one of the 12 specific interventions examined, were deemed not to provide sufficient level of evidence for their related question. The reasons for exclusion are listed in the QUORUM flow chart (Appendix D). In total, 36 records (reporting on 37 studies) were deemed relevant and provided sufficient level of evidence for the systematic review. The Evidence Tables are presented in Appendix E and provide descriptive characteristics and results from the interventions. Experimental studies are presented first followed by observational studies in the following study design order: randomized clinical controlled trials; clinical controlled trials; prospective cohorts; retrospective cohorts; case-control studies; and before-after studies.

Report and Study Design Characteristics of Included Studies

The 36 studies included 6,960 individuals, ranging in age from 19 years to 95 years. Twenty-three studies reported on percentage of male participants, which ranged from 38.2% to 76%.[67,87-108]

Stroke Type

As expected, participants with acute ischemic stroke were drawn from admitting hospitals and EDs in 26 of 34 studies (72.7%)[55,67,92-94,97,99-102,104-118] and nine of 34 studies (27.3%) admitted patients with ICH.[87-91,96,119-121] Two studies (6%) recruited patients with both ischemic and hemorrhagic stroke.[95,103]

Severity

Twenty-two studies specified the baseline severity of stroke using the NIHSS. Eighteen studies used only the NIHSS,[55,67,93,94,97,99-102,104-106,108,109,109-118] whereas, four studies used other scales in addition to NIHSS.[92,97,107,116] Four studies included patients with all severity types assessed by NIHSS ,[67,99,102,113] whereas, the remainder of the studies included subjects with moderate to severe stroke excluding mild strokes as defined by NIHSS of less than 4.[55,92-

[94,97,100,101,103,106,109-112,114-117] One study used the mRS alone,[118] seven studies used other various scales such as the Glasgow Coma Scale (GCS),[87-89,121] level of consciousness,[119] New York Heart Association grade system,[96] or clinical and neurological measures;[120] five studies did not report on the baseline severity of stroke of the subjects recruited.[90,91,95,104,105]

Quality

The quality of included RCTs (n=24) was scored using the Jadad scale (scores range from 0 to 5). Only one RCT study reported on all Jadad items.[113] Nine RCTs received only one point.[55,87,93,95,97,115,119-121] Allocation concealment was assessed as adequate in three studies,[92,111,113] inadequate in one,[93] and unclear for the remaining 20 studies.[55,67,93,94,97,99-102,104-119 55,67,87-89,94-97,99,109,110,112,114,115,120,121] One included controlled clinical trial[103] was scored using a modified version of the Jadad scale (range 1 to 3) and received a score of 1. Only one of the nine included cohort studies reported on all the NOS items,[117] for a maximum of 9 points. The remaining reports scored between 5 and 8 points.[100-102,104-106,118] One included case-control study received 8 points.[116] Three pre-post study designs were included in our review, however, the quality could not be determined.[90,91,105]

Intervention A: Does Surgery Impact the Outcome in Patients with Acute Intracerebral Hematoma?

Twenty-three studies investigating the effectiveness of surgery for ICH were identified by our searches. One relevant study was identified by an expert[122]and was published beyond our search dates. This study, along with five unique parallel RCTs met our eligibility criteria and was included in our final analyses (Summary Table 1).[87-89,119-121] Studies were published between the years 1989 and 2003. Eighteen studies were excluded for level of evidence and included one non-RCT,[123] three single prospective cohorts,[124-126] five case-control studies,[127-131] eight non-comparative case series,[132-139] and one study whose design could not be determined.[140]

Primary intracerebral hematoma has a poor outcome, with case series approaching a 50% fatality rate.[141] Hematoma growth is reported in 38% of patients in the first 24 hours, with consequent deterioration due to local pressure effects, perilesional ischemia, and toxic effects of thrombin and blood degradation products.[142] Functional outcomes substantially impaired in survivors, with only 16% of patients randomized into the ISTICH Trial having either good recovery or moderate disability, as measured by the Glasgow Outcome Scale at 6 months.[143]

Morgenstern and colleagues reported on patients with ICH from a Prospective Registry and a randomized trial in Houston between 1993 and 1996.[87] Sequential patients were initially added to the registry provided that they had hematomas greater than 9 mL in size and could be operated on within 12 hours. The registry contained a total of 41 patients, seven of whom had surgery (open craniotomy) and 34 of whom were treated medically. Surgical patients were more likely to have shorter median time from symptom onset to arrival at the ED (2.9 hours versus 5.4 hours). The median hematoma volumes were larger in patients receiving craniotomy (96.2 mL vs. 32.8 mL). In the nonrandomized group, there was a trend towards a better 6-month outcome

as measured by the Barthel Index for medically treated patients (Barthel Index score of 85 versus 65 for surgically-treated patients). This difference was not, however, significant.

The prospectively randomized group contained 34 patients. All of the patients had a lobar or deep hemispheric hematoma greater than 9 mL but less than 20 mL in size. Patients with cerebellar and brain stem hematomas were excluded. The intervention group received craniotomy with hematoma extraction. The control group was admitted to a neurological intensive care unit with ICP monitoring. Treatment including mechanical ventilation, osmotic diuretics, and ventricular drainage, was carried out as needed to maintain an ICP of less than 21 cm of water. The primary outcome measure in this randomized group was 6-month survival, which slightly favored the surgical group (81% versus 76%). This difference, however, was not significant.

The surgical patients had somewhat poorer entry Glasgow Coma Outcome Scale (GOS) scores and, therefore, there was a bias against good outcome in these patients. The trial was also significantly hampered by low power. The limited number of subjects resulted in a 50% power to detect a 4-fold decrease in 6-month mortality of 25%. Of potential importance, the medically treated group did not have a standard regimen for blood pressure, and steroid treatment was not permitted.

Teernstra et al.[88] reported on a multicenter RCT carried out in the Netherlands between 1996 and 1999 that examined the stereotactic treatment of intracerebral hematoma by means of a plasminogen activator (SICHPA). Seventy-one patients over the age of 45 with non-traumatic supratentorial hematomas with volumes of 10 mL or greater, and Glasgow eye motor scores between 2 and 10, were randomized to either the surgical group (n=36) or non-surgical (control) group (n=35). The surgical group had the intervention performed within 72 hours of onset. Treatment consisted of placement of a stereotactic catheter with 5000 IU of urokinase injected every 6 hours for eight cycles of treatment. At the end of each cycle, gentle aspiration was used to remove any liquefied hematoma. The control group was described as receiving "standard supportive care." There was no requirement for ICP monitoring. The primary endpoint was death at 6 months. Mortality at this time point was 56% in the surgical group and 59% in the medical group with no significant difference noted in a Cox Regression Analysis. The stereotactic surgery group did demonstrate lower hematoma volumes. Supportive care and baseline characteristics were similar between the two groups, with the exception that surgical patients more often received low molecular weight heparin and mechanical ventilation, and generally had a slightly lower Glasgow Coma Score on admission.

Auer et al.[119] compared endoscopic surgery within 24 hours with conservative management. One hundred patients, between 30 to 80 years of age, with hematomas over 10 cm^3 and a neurologic deficit, were randomized. All patients had supratentorial bleeds and angiograms to exclude aneurysmal hemorrhage or arteriovenous malformation. Patients randomized to surgery had a bur hole performed through which a 6 mm neuroendoscope was inserted. The scope was guided by intraoperative ultrasound. Once the probe was inserted, alternating irrigation and suction was performed under video guidance with bleeding cauterized by means of a laser within the instrument. The conservatively managed group was treated with hyperosmolar agents, cortisone, and antifibrinolytic agents. Blood pressure was kept between 140 and 160 mmHg irrespective of the presenting blood pressure. Outcome was analyzed at 6 months by means of the mortality rate and quality of survival measured on an ad hoc 6-point scale. At 6 months,

mortality was 42% in the surgical group and 70% in the medical group, which was felt to be significant. There was no overall difference in quality of survival.

Batjer et al.[120] studied 21 patients between 1983 and 1989 at a single center in Texas using a RCT design. Patients aged 30 to 75 years with putamenal hemorrhages greater than 3 cm in diameter by CT scanning, were included. All patients were required to be hypertensive, which was arbitrarily defined as a minimal recorded blood pressure within the medical record of 160/95. Patients with minimal hemiparesis, decorticate or decerebrate posturing were excluded. Three arms were studied: best medical management, best medical management plus intracranial pressure monitoring, and surgical evacuation. Medical management was rigorously defined to include Decadron, antihypertensive therapy to decrease blood pressure by 25% within 24 hours, intermittent Lasix and Mannitol with specified criteria for intubation and mechanical ventilation. The second intervention was best medical management, as defined above, with intracranial pressure monitoring. The monitor was used to modify medical intervention such that the pressure was maintained at 20 mmHg. The surgical group was treated with craniotomy, with control of blood pressure intraoperatively, and a standardized surgical approach. The trial had a pre-planned sample size of 60, but was terminated after 21 patients had been randomized, since no difference between the three treatment groups was observed, and the outcomes were felt to be poor. At 6 months, 15 of 21 patients were dead or vegetative. The numbers were felt to be too small for meaningful statistical comparison; regardless, no differences were noted between the three groups.

Juvela et al.[121] reported on the experience of 52 patients with supratentorial spontaneous intracranial hemorrhage at a single center in Finland. Patients were enrolled between 1982 and 1986. Patients with aneurysmal hemorrhage along with hemorrhage from arteriovenous malformations were excluded. Twenty-six patients were randomized to either an intervention group or non-intervention group. The intervention group had surgical evacuation within 48 hours (median 14.5 hours), whereas, the non-intervention group was treated with conservative management. No details for perioperative care or conservative management were provided. Patients in the conservative group were more likely to be basal ganglion hemorrhage. Six-month mortality was 38% in the conservative group and 46% in the surgical group with no significant difference noted. There was likewise no significant difference in a dichotomized Glasgow Outcome Scale at 6 months.

Zucarrello et al.[89] investigated early surgical treatment for supratentorial ICH in 20 patients randomized over 24 months (surgical intervention n=9, medical treatment n=11). Patients were recruited from one university and two community hospitals. Principal eligibility criteria were ICH volume >10cm^3 on baseline CT scan, GOS >4, randomization within 24 hours of symptom onset (median 3 hours 17 minutes), and <3 hours to time of surgery (1 hour 20 minutes), with no evidence of ruptured aneurysm or arterovenous malformation. No significant differences were noted for mortality rates. The likelihood of good outcome (<3 GOS) was 56% for the surgically treated group and 36% in the medically treated group, which did not differ significantly. A nonsignificant trend for good outcome for the surgically treated group for median GOS, Barthel Index, and Rankin Scale was observed at 3-month follow up. A significant difference in favor of surgical intervention for the NIHSS score was also observed (p=0.04).

Summary Table 1. Intervention A

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Auer, 1989 Austria[119]	RCT Parallel	n=100 Inclusion Criteria: Acute, hematoma >10 cm^3; within 48 hr of hemorrhage with neurological deficits, consciousness impairment; age between 30-80 y; appropriate for surgery / angiography Baseline Differences: NR Comments: Small sample size in subgroup analyses; methods of randomization unclear; good outcome more frequent in alert/ somulent patientsthan in stuporous/comatose pts	I: Surgery for ICH, (n=50) C: Medical tx (n=50)	▪ Significant.y lower mortality rate at 6 months ▪ Signficantly better outcome (unique scale)
Batjer, 1999 US[120]	RCT Parallel	n=21 Inclusion Criteria: Acute hypertensive putaminal ICH ≥ 3cm in diameter; moderate to severe hemiparesis/ uniform hemiplegia (grade 1-3); < 24 hr post onset Baseline differences: No significant differences between groups Comments: Enrolment ceased prior to reaching target . As Outcome of all groups felt to be unacceptably poor. Selection criteria allowed only severely disabled patients, with large hematomas to be admitted. These characteristics may have further heightened management morbidity	I: Surgery for ICH (n=8) C1: Best medical management (n=9) C2: Best medical management + intracranial pressure monitoring (n=4)	▪ No significant difference in mortality outcomes ▪ No significant difference in outcome status

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Summary Table 1. Intervention A

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Juvela, 1989 Finland[121]	RCT Parallel	n=52 Inclusion Criteria: Acute ICH within 24 hr post bleed; unconscious &/or severe hemiparesis or dysphasia Baseline differences: More combined thalamic & basal ganglionic hematomas & hematomas with intraventricular extension in the surgical group Comments: Quality of life remains poor although surgery improves the length of survival in semicomatose or stuporous pts	I: Surgery for ICH (n=26) C: Conservative tx (n=26)	▪ Significant difference in mortality rate at 6 months within the GCS 7-10 subgroup ▪ No significant difference in morbidity
Mendelow, 2005 UK[122] (reviewer nominated; published beyond search dates)	RCT Parallel	n=1033 Inclusion Criteria: CT evidence of spontaneous supratentorial ICH, within 72 hr; uncertainty by neurosurgeon about benefits of either tx; hematoma ≥ 2 cm; GCS≥5 Baseline differences: NR Comments: Cross over from IG to CG n=31; from CG to IG n=140	I: Surgery for ICH (n=503) C: Conservative tx (n=530)	▪ No significant difference at 6 mos mortality ▪ No significant difference at 6 mos functional outcomes (BI, mRS)
Morgenstern, 1998 US[87]	RCT Parallel	n=34 Inclusion Criteria: Acute ICH <9 mL; diagnosed by CT within 3 hr screening, <12 hr; GCS 5-15 Baseline differences: Deep ICH (94% putaminal in surgical group vs. 59% putaminal in medical group) Comments: Small sample size; 1 pt randomized to medical group crossed over to surgical arm; 1 pt randomized to surgical arm excluded (surgeon refused to randomize)	I: Surgery for ICH (n=17) C: Standard medical tx (n=17)	▪ No difference in 1 or 6 month mortality or 6 mo BI score

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Summary Table 1. Intervention A

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Teernstra, 2003 The Netherlands[88]	RCT Parallel	n=71 Inclusion Criteria: Patients with expected mortality of 88%; age >45 y; ICH >10 cm^3; within 72 hr of ictus, Glasgow eye motor score 2-10 Baseline differences: More cardiovascular disease history in surgical group (NS) Comments: Small sample size; improved mortality rate in conservative group possibly due to increased supportive care or an specific selection bias	I: Surgery for ICH (n=36) C: No- Surgery (n=35)	▪ No significant difference (6 months) mortality rate ▪ No significant difference mRS (at 6 months) ▪ Significant ICH volume reduction intervention group
Zuccarello, 1999 US[89]	RCT Parallel	n=20 Inclusion Criteria: Acute supratentorial ICH >10 cm^3, diagnosed by CT, with focal neurological deficit; age >18y; GCS >4, within 24 hr of onset; surgery within 3 hr of randomization Baseline differences: No significant differences Comments: Only 10% of patients admitted met eligibility criteria; some patients were not entered because of reluctance of surgeon to randomize	I: Surgery for ICH (n=9) C: Control (n=11)	▪ No significant difference in mortality at 3 mo ▪ No significant difference in BI score at 3 mo ▪ Significant difference for NIHSS at 3 mo ▪ Lower ICH volume in the IG

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Intervention B: Does Antihypertensive Treatment Reduce Stroke Related Mortality and Disability in Patients with Acute ICH?

Six studies were identified that investigated antihypertensive therapy for ICH.[90,91,144-147] Four studies were non-comparative case series designs and were excluded from our review.[144-147] Two unique studies met eligibility criteria for investigating the effectiveness of antihypertensive therapy for ICH and were a pre-post design (Summary Table 3).[90,91] The year of publication for each study was 1993[90] and 2000.[91] Neither of these studies prospectively answers the clinical question posed but they were included to provide insight into relevant surrogate and safety measures.

Kay et al.[90] reported a non-randomized uncontrolled clinical trial evaluating the efficacy of the serotonin antagonist, ketanserin, and its antihypertensive properties to lower mean arterial pressure in patients with ICH without a subsequent rise in ICP.[90] Ten patients, five men and five women aged 49 to 64 years, were recruited from the Chinese University of Hong Kong. All patients had a spontaneous ICH confirmed by CT scan 8 to 48 hours prior to recruitment, a systolic BP >180 mm Hg and/or a diastolic BP >100 mm Hg, no previous history of hypertension, and required ICP monitoring in the intensive care unit. The patients were sedated, paralyzed, endotracheally intubated and mechanically ventilated to a target $PaCO_2$ of 30 to 34 mm Hg. An intravenous bolus of 5 to 10 mg ketanserin was given and radial arterial pressure and ICP were measured continuously. BP readings were performed at multiple time points and compared with pre-injection pressures using analysis of variance (ANOVA) with a correction for multiple comparisons.

After the intravenous bolus of ketanserin the BP decreased on average by 40/21 mm Hg within 5 minutes and increased gradually over the next 2 hours remaining below pre-treatment levels. ICP remained stable throughout the observation period and thus the calculated CPP decreased by a mean of 27 mm Hg after 5 minutes, and on completion of the study, steadily increased to be 13mmHg below the pre-treatment value. There was no evaluation of clinical outcomes reported in this study.

A more recently published study by Nishiyama et al.[91] explored the safety of calcium antagonist nicardipine and its effect on mean arterial pressure, ICP, and CPP. Twenty-two patients with an acute hypertensive putaminal hemorrhage requiring surgical drainage were recruited for a non-randomized uncontrolled clinical trial. There were 14 men and eight women ranging in age from 47 to 79 years. Mechanical ventilation was continued post-operatively to a target $PaCO_2$ of 30 to 35 mm Hg. Post-operatively nicardipine infusion was started at 1 µg/kg/min with rate adjustments to target systolic blood pressure between 120 to 160 mm Hg (a 20%-30% reduction from pre-infusion levels) for 72 hours. In addition all patients received: a hyperosmolar solution (glycerin fructose), anti-seizure medication (phenytoin) and antibiotics. BP was measured directly via a radial artery catheter and ICP monitored continuously via by an intraventricular catheter. Middle cerebral artery blood flow velocity (Vmca) and pulsatility index (PI) were measured and calculated using Transcranial Doppler Ultrasound. Platelet counts were also monitored as an anti-platelet effect of calcium antagonists has been previously reported and may increase the risk of bleeding.[148] Clinical outcomes included level consciousness using the Japan Coma Scale (included in the appendix of the article, not referenced elsewhere) and repeat CT imaging to evaluate extension of hemorrhage.

Patients' BP decreased during and up to 24 hours after the end of the Nicardipine infusion compared with pre-infusion. There was no difference in platelet counts. Vmca and PI were unchanged and ICP decreased 24 hours after the end of the infusion. CPP was decreased at 24 and 72 hours of the infusion but was greater than 50 mm Hg at all times. Consciousness levels were unchanged and CT findings did not show any exacerbation of bleeding or edema.

Summary Table 2. Intervention B

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Kay, 1993 Hong Kong[90]	Pre-post	n=10 Inclusion Criteria: ICH confirmed by CT 8-48 hr pre-recruitment; systolic BP >180 mm Hg, diastolic BP >100 mmHg Baseline Differences: No significant differences between groups Comments: No evaluation of clinical outcomes	I: Antihypertensive therapy for ICH (n=10)	▪ Systolic arterial pressure lower in IG ▪ Calculated cerebral perfusion pressure decreased
Nishiyama, 2000 Japan[91]	Pre-post	n=22 Inclusion Criteria: Acute putaminal hemorrhage secondary to hypertension, with surgical drainage of hematomas Baseline Differences: No significant differences between groups Comments: Weak study due to lack of control group & small sample size	I: Antihypertensive therapy for ICH (n=22)	▪ Significant decrease in blood pressure ▪ CPP decreased at 24 and 72 hours

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index; CPP = cerebral perfusion pressure

Intervention C: Does IA thrombolysis reduce stroke-related mortality and disability in adults with acute ischemic stroke?

A total of 37 studies investigating IA thrombolytic therapy for ischemic stroke were identified by our searches. Nine single prospective cohort studies,[149-157] one controlled clinical trial,[158]13 non-comparative case-series,[159-171] two case studies,[172,173] four abstracts[174-177] and three studies in which designs could not be determined[178-180] were excluded from our final analyses. Five unique studies met our eligibility criteria for inclusion (Summary Table 3).[92-94,109,110] All five studies were parallel RCTs and were published between 1999 and 2001.

Del Zoppo and colleagues[110] described the results of the PROACT I study, a North American multi-centre study of IA pro-urokinase compared with placebo, carried out between 1994 and 1995. Patients aged 18 to 85 with new onset focal neurologic signs, and NIHSS scores between 4 and 30, were randomized on a 2:1 basis to either 6 mg pro-urokinase plus heparin (100 IU/kg bolus plus 1000 IU/hour infusion) or saline placebo plus matching heparin. After reviewing the

results on the first 16 patients, the External Safety Committee changed the infusion to 2000 IU bolus followed by 500 IU/hour for 4 hours. Recanalization rates in the M1 or M2 vessels at 120 minutes, defined as TIMI 2 or 3 or better, were 57.7% in the treated group versus 14.3% in the control group. There was, however, no significant difference between mortality or mRS scores (either 0 or 1) at 90 days.

The results of the PROACT I trial were used to design PROACT II, which was reported by Furlan and colleagues.[92] This trial was conducted between 1996 and 1998 in North America. A total of 12,323 patients were screened, resulting in 474 patients subjected to angiogram, and 180 patients randomized after meeting angiographic criteria. Eligible patients had clinical signs of less than 6 hours in duration in the middle cerebral artery (MCA). The NIH Stroke Scale Score was 4 to 30. Patients with isolated aphasia or hemianopsia were excluded. The CT scan excluded bleed or tumor and demonstrated early infarct signs in less than one third of the MCA territory. A diagnostic cerebral angiogram had to show complete occlusion or minimal perfusion (TIMI grade 0 or 1) in the M1 or M2 branches of the MCA. Dissection or severe carotid stenosis were exclusionary criteria. Randomization was on a 2:1 schedule favoring the intervention. One hundred and twenty-one patients received 9 mg of IA pro-urokinase over 2 hours. Heparin was delivered at a 2000 IU unit bolus followed by a 500 IU/hour infusion in all patients. The pro-urokinase was injected intra-thrombus or in the proximal face of the thrombus. Clinical assessments were blinded and the primary outcome was a mRS score of less than 2 at 90 days. This outcome was achieved by 40% of the treatment group compared with 25% of the control group ($p=0.04$). The calculated number needed-to-treat, on the basis of the absolute difference, was seven. Intracranial hemorrhage within 24 hours occurred in 35% of patients in the treated group compared with 13% in the control group. It should be noted that the control group contained more patients with diabetes than the treatment group (20% versus 8%).

Kase and colleagues[109] presented the subgroup analysis of PROACT II regarding bleeding. The group who received treatment (n=110) versus the group that received no treatment (n=64) was compared. Symptomatic intracranial hemorrhage occurred in 12 of the 110 patients (10.9%) treated with urokinase with a mean onset time of 10 hours after initiation of treatment, compared with two of the 64 patients (3.1%) in the control group. Mortality with symptomatic ICH was 83%. Elevated blood glucose was associated with symptomatic intracranial hemorrhage, particularly if the baseline glucose was greater than 200 mg/dL (11.1 mmol/L). This resulted in a relative risk of bleeding of 4.2 (95% CI 1.04-11.7).

The EMS Bridging Trial was reported by Lewandowski and colleagues.[94] This trial was a Phase I trial conducted between 1995 and 1996 in several centers in the United States. Patients with acute stroke (within 3 hours of symptom onset) and NIHSS scores greater than 5, and were CT-negative for hemorrhagic lesion, were enrolled. The interventional group received IV tPA 0.6 mg/kg plus IA tPA; the latter was delivered if a thrombus was seen on angiogram. The control group received IV placebo plus IA tPA (1 mg) injected beyond the thrombus with subsequent retraction into the thrombus followed by 10 mg/hour tPA infusion. Blood pressure was maintained less than 180/105. The calculated sample size was 30 patients per arm; however, only 35 were recruited prior to the study being halted. The primary outcome was a decrease of 7 or more points in the NIH Stroke Scale from baseline to 7 to 10 days, or a NIH Stroke Scale Score of 0 to 1 at 7 to 10 days. This outcome was achieved by 24% of the population in both

groups. There was also no difference in the 90-day Glasgow Outcome Score, Barthel Index Score (95-100), or mRS Score (0 or 1).

Keris et al.[93] combined IV and IA treatment in a single-center study performed in Latvia between 1997 and 1998. Patients with ischemic stroke of less than a 6-hour duration in the internal carotid distribution were included. Edema and effacement were described as exclusion arms; however, explicit exclusion criteria were not given. Intervention cases received 25 mg of tPA IA at the proximal surface of the clot followed by 25 mg IV tPA plus 5000 IU heparin initially and twice a day. Analysis was performed on those who had received the intervention (n=12) versus those who had received no intervention (n=33). A good outcome was defined as a mRS score of between 0 and 3. This outcome was obtained at 12 months by 10 of the 12 patients in the treatment arm and 11 of the 33 patients in the control arm. Fatal bleeding was noted in two patients, both of whom were in the combined treatment arm. Symptomatic ICH occurred in two patients in the combined treatment arm and 1 in the placebo/IA treatment arm. These rates were not significantly different between the two arms. Other systemic bleeding complications did not differ between the two arms. Hemorrhage was noted in two of 12 (17%) patients in the intervention group. The authors concluded that, in spite of baseline differences in the two groups, the outcome suggested a benefit for IA treatment.

Summary Table 3. Intervention C

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
del Zoppo, 1998 US & Canada[110]	RCT Parallel	n=40 Enrolment window: Feb 1994 - Feb 1995 Inclusion Criteria: Acute carotid artery stroke; new focal neurological signs in the MCA within 6 hr of onset, NIHSS score ≥4; (except for isolated aphasia or hemianopsia; age 18-85y) Baseline differences: No significant differences between groups Comments: Small sample size; randomization scheme 2:1 (IG vs. CG); phase 2 trial Safety and dose finding	I: IA Urokinase (n=26) C: Placebo (n=14)	▪ No significant difference in mortality ▪ MCA recanalization significantly better than IG ▪ No significant difference in functional outcomes (mRS, BI, & NIHSS)
Furlan, 1999 US & Canada[92]	RCT Parallel	n=180 Enrolment window: Feb 1996 - Aug 1998 Inclusion Criteria: Acute IS (MCA), 18-85 y; with new neurological symptoms < 6 hr post onset; NIHSS score ≥ 4 Baseline differences: Baseline diabetes in CG; more ECASS CT protocol violation in IG Comments: All secondary outcomes favored intervention with no statistically significant results	I: IA Urokinase (n=121) C: Placebo (n=59)	▪ No significant mortality at 90 d ▪ Significant improvement in proportion of patients with mRS ≤ 2at 90 d ▪ Recanalization significantly better in IG (66% vs. 18%) ▪ Increased symptomatic ICH in IG (10% vs. 2%)

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Summary Table 3. Intervention C

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Kase, 2001 US[109] (serial publication of[92])	RCT Parallel	n=174 Enrolment window: NR Inclusion Criteria: Acute IS M1 or M2 segments of MCA < 6 hr post onset; NIHSS score 4-30 Baseline differences: No significant differences between groups Comments: Higher rates of symptomatic ICH in IG (10.9%) compare to that of CG (3.1%)	I: IA Urokinase (n=110) C: Placebo (n=64)	▪ Mortality following symptomatic ICH (83%) ▪ Serum glucose >200 mg/dl increases risk of hemorrhage
Keris, 2001 Latvia[93]	RCT Parallel	n=45 Enrolment window: Feb 1997- Mar 1998 Inclusion Criteria: Acute severe hemiparetic IS within 6 hr post onset Baseline differences: Large CG compare to IG (n=33 vs. n=12) Comments: unbalanced groups due to randomization before consent; no significant benefit with tx despite baseline differences	I: IV plus IA tPA (n=12) C: Conventionnel tx (n=33)	▪ Chi^2 for mRS & mortality
Lewandowski, 1999 US[94]	RCT Parallel	n=35 Enrolment window: February 1995 – March 1996 Inclusion Criteria: Acute focal IS within 3 hr of symptom onset (based on NINDA tPA stroke study) Baseline differences: NIHSS scores significantly higher in IG Comments: Small sample size; number of subjects completing all follow ups for each group is not specified	I: IV+IA tPA (n=17) C: Placebo+ IA thrombolytic tx (n=18)	▪ No difference in mortality ▪ No difference in functional outcome at 3 mo ▪ Arterial recanalization better in the IV+IA group

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Intervention D: Does Treatment to Normalize Blood Glucose Levels Reduce Stroke Related Mortality and Disability in Adults with Acute Stroke?

Our searches identified two unique studies investigating the effects of normalization of blood glucose levels in patients with ischemic stroke (Summary Table 4).[95,96] Both studies were parallel RCTs and were published in 2004 and 1999, respectively.

Post-stroke hyperglycemia has been identified in previous studies as being associated with poor stroke outcome. It is unclear to what extent this is a "normal" physiological response or whether it may lead to increased cerebral damage in the acute phase. The Glucose Insulin in Stroke Trial (GIST) has resulted in two published studies in this area. First, a Pilot study[96] evaluating the feasibility of a large multicenter RCT of glucose, potassium, and insulin (GKI) in patients with acute stroke. Second, a small RCT that evaluated the natural history of post-stroke hyperglycemia and the immediate response to GKI.[95]

The pilot study[96] was a non-blinded RCT from a single center. All patients who presented with an acute stroke within 24 hours of symptom onset and had a plasma glucose of 7.0 to 17.0 mmol/L were eligible. Exclusion criteria included: New York Heart Association (NYHA) grade 3 or 4 heart failure; renal failure (creatinine level >200 μmol/L); anemia (Hb <9 g/dL); radiologically documented pneumonia; coma (Glasgow Coma Scale motor subscore <4); previous disabling stroke (mRS Score >3); dementia; isolated posterior circulation stroke without physical disability; pure language disorder; previously diagnosed insulin-treated type 1 or 2 diabetes; or, subarachnoid hemorrhage.

Two hundred and forty-five consecutively admitted patients were screened over a 7-month period. Of these, 53 patients were randomized—28 to active treatment (with three patients withdrawn as stroke was not confirmed by post-randomization CT) and 25 to control treatment. Active treatment consisted of a combined infusate of 500 mL 10% dextrose, 16 U Human soluble insulin (Actrapid; Novo nordisk) and 20 mmol potassium chloride (KCl) administered through a peripheral vein at a fixed rate of 100 mL/h to a maximum volume of 2400 mL. Glucose testing was performed hourly by glycaemic strip aiming for a target glucose of 4 to 7 mmol/L. Above the target range, 4 U insulin was added to the infusate. Below the target range, the infusate was stopped and glucose repeated in 15 minutes interval 50% dextrose was given intravenously if glucose ≥4 mmol/L was not achieved spontaneously in 30 minutes. When target range was achieved, the infusate was restarted with 4 fewer units of insulin. Control treatment consisted of 154 mmol/L saline at 100 mL/h to a maximum volume of 2400 mL. Glucose values were not treated unless they exceeded 17 mmol/L.

Baseline blood work, BP and pulse were measured every 4 hours, and plasma glucose samples were measured every 8 hours during the 24 hours of infusate. All blood work was repeated at 48 hours. Clinical assessments of neurological impairment (European Stroke Scale (ESS)) and activities of daily living (Nottingham Extended Activities of Daily living for function) were performed at baseline, 24 hours, 48 hours, 7 days and 4 weeks by trained observers. Clinical assessments were not blinded to treatment allocation

The average glucose level in the group as a whole at randomization was 9.1 mmol/L. The glucose values for the GKI group were 6.4, 6.5, and 6.9 mmol/L at 8, 16, and 24 hours, respectively. For the control group, the values were 7.6, 7.2and 7.6 mmol/L, respectively. These differences did not achieve statistical significance. In the active treatment group the insulin concentration had to be adjusted at least once in 23 of 25 patients. Five patients required single doses of 10% dextrose for low glucose values although only one patient was symptomatic. There was no difference in clinical outcomes between the two groups.

The GIST-UK trial[95] was a multicenter RCT. The eligibility and exclusion criteria were similar to the pilot study with the following exception that entry was based on plasma glucose levels of 6.0 to 17.0 mmol/L. Clinical outcomes were not measured in this study, as the focus was natural history of acute hyperglycemia in managed stroke care and efficacy, safety and practicability of routine intervention.

The first 452 patients recruited had a mean age of 74.8 years and 53.3% were women. Overall mean admission plasma glucose was 8.37 mmol/L (SD 2.13); of note, 28.3% of the patients had a glucose level of between 6.0 and 6.9 mmol/L at admission. Baseline demographics were the same between groups. Of the recruited patients, 221 were randomized to receive GKI and 231 received saline solution. Plasma glucose values were significantly lower in the GKI group at 8, 16 and 24 hours of infusion. In both groups, the glucose values were significantly lower during the active or control infusion as compared to baseline. Adjustment of the GKI regimen was required a median of two times per patient. Twenty cases of hypoglycemia occurred that required treatment with 10% dextrose. Diabetic patients within the GKI group required significantly more insulin to reach target, as well as more changes overall compared with non-diabetic patients in the GKI group.

Summary Table 4. Intervention D

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Gray, 2004 UK[95]	RCT Parallel	n=452 Inclusion Criteria: Acute stroke< 24 hr post onset, with admission glucose level > 6 to <17 mmol/L Baseline differences: No significant differences between groups Comments: Study was not reported as blinded; no CT in 36 patients; target capillary blood glucose level 4 - 7 mmol/L for the duration of infusion	I: Normalization of blood glucose levels for IS (n=221) C: Control (n=231)	▪ Significant difference in mean plasma glucose values at subsequent time intervals in 24 h
Scott, 1999 UK[96]	RCT Parallel	n=53 Inclusion Criteria: Acute IS with neurological deficit lasting > 24 hr; age > 18 y; within 24 hr of onset Baseline differences: No significant differences between groups reported Comments: Small numbers with multiple outcome tests; no measure of severity of stroke at randomization; study was not blinded; 2 crossover from CG to IG; 3 patients in IG removed for protocol violations	I: Normalization of blood glucose levels for IS (n=28) C: Control (n=25)	▪ No Significant difference in serum glucose levels

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Intervention E: Does Mechanical Thrombus Disruption Reduce Stroke-Related Mortality and Disability in Adults with Acute Ischemic Stroke?

Ten studies investigating the effectiveness of mechanical thrombus disruption for ischemic stroke were identified by our searches. One study was identified by an expert and screened for inclusion.[111] This study was published beyond our literature search dates. One case-control,[181] five non-comparative case series,[182-186] and three studies in which the design could not be determined,[187-189]were subsequently excluded from our review. Two unique parallel RCTs, which met our eligibility criteria, were included in our final analyses (Summary Table 5).[97,111] These studies were published in 2003 and 2004, respectively.

Eggers et al. reported on a single-center, prospective RCT, of ultrasound-enhanced thrombolysis in MCA occlusion.[97] The study was carried out between 2000 and 2002, and involved individuals with ischemic stroke of less than 3 hours duration in the MCA territory. All participants met the criteria for the NINDS Thrombolysis Protocol and had a M1 occlusion diagnosed by transcranial ultrasound. tPA was given as per the NINDS Protocol.[49] The intervention group received continuous transcranial color-coded sonography. The monitoring was in the pulse wave Doppler mode with an instrument developing an acoustic power of 179 mW/cm^2. The control group had patency of the vessel established by transcranial sonography at baseline, 20, 40 and 60 minutes. Each assessment lasted less than 2 minutes.

Of the 1,177 candidates screened, 25 met the inclusion criteria. Of these, 11 were randomized to the treatment group and 14 to the control group. Exclusions were due to failure to meet the NINDS treatment criteria or an absence of an MI occlusion. The primary efficacy parameters at 90 days included the Barthel Index, mRS Score and mortality. Six of the 11 patients in the treatment group (54.5%) and 1 of 14 patients in the control group (7.7%) met the pre-specified criteria of Barthel greater than or equal to 95 (p=0.037). There was, however, no difference between the two groups in the 90-day mRS score or in mortality. The treated group demonstrated a higher median peak systolic blood flow velocity at the end of 1 hour of treatment. However, there was no significant difference in recanalization between the two groups. Four patients in the treated group experienced intracranial hemorrhage or hemorrhagic transformation of the infarct, compared with one patient in the control group (p=0.14).

Alexandrov and colleagues reported on the results of the CLOTBUST Study.[111] This phase II multicenter trial was carried out in North America on patients treated with IV tPA within a 3-hour window. One hundred and twenty-six patients were randomized to receive either placebo or continuous ultrasonography. Head frames were placed on all patients. The patients in the treatment group began ultrasonographic monitoring prior to the administration of the tPA bolus and for the subsequent 2 hours. Emitted power output was set at the maximal achievable level with selected insonation depths under the FDA allowed threshold of 750 mW. In both groups, follow-up measurements were taken 30, 60, 90 and 120 minutes after the tPA bolus with arterial recanalization defined by Doppler criteria. The groups were comparable at baseline and equal in number (n=63 for each arm). Symptomatic intracranial hemorrhage occurred in three patients in each group. The pre-specified endpoints were complete recanalization or early or dramatic recovery from stroke. The latter was defined as a reduction of 10 or more points in the NIHSS or a total NIHSS of 3 or less within 2 hours after administration of the tPA bolus. Thirty-one patients (49% of the treated group) and 19 patients (30% of the control group) reached the pre-specified endpoints (p=0.03). Re-occlusion within 2 hours occurred in 11 patients in the treated group (18%) and 14 patients in the control group (22%, p=0.7). The 3-month mortality rates were 15% and 18% in the treated and controlled groups, respectively (p=0.4). Follow-up at 3 months was incomplete by four patients who were excluded from the outcome analysis. mRS scores of 0 or 1 were present in 22 of 53 treated patients (42%) and 14 of 49 control patients (29%) (relative risk 1.45; 95% CI 0.84-2.51; p=0.2).

Summary Table 5. Intervention E

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Alexandrov, 2004 US & Canada[111]	RCT Parallel	n=126 Inclusion Criteria: Acute IS of MCA, within 3 hr post onset; IG: Abnormal flow through MCA, with TIBI scale grade 0-3 (Thrombolysis in Brain Ischemia flow-grading system) before tPA tx Baseline differences: No significant differences between groups Comments: Additional IA tPA with mechanical manipulation n=9 (14%) in IG & n=11 (18%) in CG underwent additional IA tPA of thrombus with no effect on outcomes	I: Mechanical thrombus disruption for IS (n=63) C: Control (n=63)	▪ Complete recanalization or dramatic clinical recovery significantly better in IG
Eggers, 2003 Germany[97]	RCT Parallel	n=25 Inclusion Criteria: Acute IS in MCA/ M1; 18-80 y, within 3 hr symptom onset (according to NINDS criteria) Baseline differences: No significant differences between groups Comments: Small sample size	I: Mechanical thrombus disruption for IS (n=11) C: Control (n=14)	▪ Significantly better functional outcome in IG (BI at 3 mo)

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Intervention F: Is the Effectiveness and Safety of Thrombolytic Therapy for Adults with Acute Ischemic Stroke Affected by Time From Onset to Treatment?

Six parallel RCTs (in seven publications) relevant to the timing of thrombolytic therapy for ischemic stroke published between 1993 and 2002 met our eligibility criteria (Summary Table 6).[112] While these studies did not directly compare outcomes stratified by timing of therapy, they cover relevant time windows and examination of the results is instructive to the question posed.[55,67,99,107,108,112,113] Albers et al.[99] is considered to be a re-analysis of Clark et al.[112] and Clark et al.[67] Two abstracts,[190,191] one multiple prospective cohort study,[192] one single prospective cohort study,[193] and one case series,[194] were excluded from our synthesis for level of evidence. No one publication investigated the link between onset to treatment time (OTT) and outcome. The included studies recruited patients across relevant time windows and in concert inform decision making on the relationship between time and outcome.

The use of tPA was well-established for the 0 to 3 hour time window by the NINDS Trial.[49]. This publication is well described elsewhere in this document. The initial trial publication did not describe an effect of time-to-treatment on treatment outcomes. A subsequent reanalysis[55], along with the results of trials using tPA outside the 3-hour window, have been reported.

Hacke and colleagues report on a trial of Intravenous tPA for acute hemispheric stroke.[108] A total of 620 patients were randomized to receive rtPA at a dose of 1.1 mg/kg versus placebo. This dose of tPA is higher than in the NINDS Trial.[49] Adults with hemispheric stroke syndromes presenting within six hours were included. Those with rapidly improving symptoms or minor deficits, as defined by a Scandinavian Stroke Scale Score of greater than 50, were excluded as were those with increased risk for bleeding. Major early infarct changes including swelling of the affected hemisphere or changes in greater than 33% of the MCA territory were also excluded. All CT scans were read in a blinded fashion independently subsequent to randomization. The primary endpoint was clinical outcome as defined by the Barthel Index and Modified Rankin Score (mRS) at 90 days. The intention to treat analysis showed no difference in either the Barthel Index or Modified Rankin Score at 90 days. A secondary endpoint of the combined Barthel Index and mRS showed a significant difference in favor of the rtPA group. One hundred and nine patients were identified as having major protocol violations, 66 of these being violations of the CT inclusion criteria. More protocol violators were in the rtPA group. Neither mortality nor intracranial hemorrhage differed significantly between the two groups on the Intention to treat analysis.

The same group reported a second trial of 800 patients from centers in Europe, Australia and New Zealand randomized to receive intravenous tPA at 0.9 mg/kg or matching placebo within six hours of stroke onset.[107] The inclusion/exclusion criteria were similar to those reported above. Four hundred and nine patients were randomized to the tPA group with 391 in the placebo group. The primary endpoint was proportion of patients with a mRS of 0 or 1 at 90 days. Subjects were recruited between 1996 and 1998. While an absolute difference of 3.7% in the proportion having an mRS score of 0 or 1 was noted in favor of tPA treatment, this difference was not statistically significant. Thirty and 90 day mortality did not differ between these two groups. During the first seven days there were more deaths in the treatment group from intracranial hemorrhage, and the combination of cerebral edema and intracranial hemorrhage. Parenchymal hemorrhage within the first seven days was more common in the tPA-treated group than in the placebo group (11.8 versus 3.1%). Symptomatic intracranial hemorrhage also occurred more often in the tPA-treated group (8.8% versus 3.4%).

Clark et al. reported the results of the rtPA 0- to 6-hour acute Thrombolytic Therapy in Acute Ischemic Stroke Study, Part A.[112] This was a multi-center North American Trial that ran from 1991 to 1993. It included patients between the ages of 18 to 79 with acute ischemic stroke of less than 6 hours' duration. A CT scan was required to exclude hemorrhage. Patients with minor stroke (score of less than 4 on the NIH Stroke Scale) along with rapidly improving symptoms were excluded. Patients with CT evidence of mass effect with midline shift were also excluded. This was a phase II trial with three planned safety and futility analyses at 75, 150 and 225 patients. The trial was stopped on the basis of an interim safety analysis in October 1993 due to safety concerns in the 5 to 6 hour window. This paper reports the results of the 142 patients enrolled until that point. The mean time-to-treatment in this group was 4 hours 17 minutes in the placebo arm and 4 hours 24 minutes in the tPA arm. Only 17% of the placebo

group and 14% of the tPA group were treated in less than 3 hours, whereas, 34% of the placebo group and 31% of the tPA group were treated between 5 and 6 hours. Patients in the placebo group were more likely to be diabetic. A dose of tPA of 0.9 mg/kg following the dosage schedule of the initial NINDS trial[49] was used.

The primary planned efficacy endpoints of 30 or 90 days showed no difference in the percent of patients who achieved a greater than 4-point decrease on the NIH Stroke Scale at 30 days, though there was a significant difference at 24 hours with 40% of rtPA patients achieving this response versus 21% of placebo patients (p=0.02). Likewise, there was no significant difference in the infarct volume. Symptomatic bleeding was more likely in the tPA group by day 10 (11.3% versus 0% in the placebo group, p=0.003). There was likewise an increased death rate in the treated group at 90 days (22.5% versus 7.0% placebo, p=0.009). In the 5 to 6 hour population, by day 10 symptomatic intracranial hemorrhage was found in 18.2% of the treated group versus 0% of the placebo group (p=0.03). Death by 90 days was present in 36% of the tPA-treated group versus 4.2% of the placebo group (p=0.01). The trial continued to enroll patients in the 3 to 5 hour window and results are reported in a separate publication.

Subsequently, Clark et al.[67] published data on the use of rtPA (Alteplase) for ischemic stroke administered within 3 to 5 hours after symptom onset. This phase 3, placebo-controlled, double-blind RCT was conducted between December 1993 and July 1998, with 90 days of follow-up measurement. Patients were recruited from 40 community and university hospitals in North America. Six hundred and thirteen (intent-to-treat) subjects with ischemic stroke were enrolled. Of these, 547 subjects were treated, as assigned, within 3 to 5 hours of symptom onset. A total of 39 other subjects were treated within 3 hours of symptom onset, 24 were treated more than 5 hours from symptom onset, and three subjects never received study medication. Subjects were administered 0.9 mg/kg of rtPA (n=272) or placebo (n=275), administered intravenously over a 1-hour period. Neurologic (NIHSS score $\leq$1) and functional (Barthel Index, mRS, Glasgow Coma Scale) outcomes were assessed up to 90 days follow-up. Thirty-two percent of placebo patients and 34% of the rtPA patients had excellent recovery at 90 days follow-up. Within the first 10 days of treatment with rtPA, there was a significantly increased rate of symptomatic ICH (7.0% vs. 1.1% for placebo, p<0.001). Mortality at 90 days was not significant between groups (11.0% in the treatment group and 6.9% in the placebo group). Results in the intent-to-treat population were similar.

A reanalysis of subjects (n=61) enrolled in the Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS) study was conducted by Albers and colleagues in 2001.[112] Patients had been randomized to receive either IV tPA or placebo within 3 hours of symptom onset. The pre-specified primary and secondary hypotheses of the ATLANTIS part B trial were used to evaluate clinical outcomes in these patients. The authors noted that although there was a significant increase in symptomatic intracranial hemorrhage, patients receiving IV tPA were more likely to have favorable outcome measured by NIHSS ($\leq$1) at 90 day follow-up compared with placebo (p=0.01).

Haley and colleagues reported results of a pilot RCT of tPA for acute ischemic stroke conducted at three centers in the U.S. between 1990 and 1991.[113] This was a feasibility trial prior to NINDS and was stratified into the 0 to 90 minute and 90 to 180 minute windows. Patients with a diagnosis of ischemic stroke verified by CT scan with a measurable neurologic deficit on the NIH Stroke Scale were included. Patients with minor stroke consisting of only

sensory loss or ataxia were excluded. TPA was delivered in a dose of 0.85 mg/kg over 60 minutes, while a matching placebo was delivered to the control group.

Twenty-seven patients were randomized, 20 (10 rtPA, 10 placebo) to the time stratum from 0 to 90 minutes and 7 (4 rtPA, 3 placebo) to the time stratum of 90 to 180 minutes. While the median stroke scale scores in the early group were comparable, the median stroke scale score in the 90 to 180 minute stratum was 14 in the placebo arm and 6 in the tPA arm. No significant difference was found in change of NIH Stroke Scale score from baseline. No intracranial hemorrhage was noted in either the tPA or placebo group in the less than 90 minute time stratum. Small numbers in the later time stratum (i.e., 90 to 180 minutes) included one of three patients who died of ICH in the placebo group; none of the four patients in the tPA group died.

Marler and colleagues reported on a reanalysis of the relationship between onset to treatment time and outcome at 3 months, early improvement in 24 hours, and intracranial hemorrhage within 36 hours.[55] The initial NINDS Report[49] suggested that there was no difference between the 0 to 90 minute and the 90 to 180 minute stratum. This subsequent reanalysis was prompted by the concern that other variables may have masked this association. The NINDS Study was a multi-center RCT that enrolled patients between 0 and 180 minutes of stroke onset to rtPA treatment (0.9 mg/kg delivered as a 10% bolus followed by 1-hour infusion) or to matching placebo. Patients with ischemic stroke scale scores greater than 4 were included. The trial was performed in two parts with identical protocols, with the exception that the primary outcome for Part A was at 24 hours, whereas, that for Part B was at 3 months. A favorable outcome was defined as minimal or no deaths that measured on a composite scale at six months while a 4-point improvement in the NIH Stroke Scale Score was considered favorable at 24 hours. The analysis of time from onset to treatment demonstrated that within the 0 to 90 minute stratum, there was a tendency to cluster between 80 and 90 minutes prior to receiving treatment. There was a similar trend, though less marked, in the 90 to 180 minute stratum. The delay from ED arrival to treatment, however, was longer in the latter time window. No association was noted between onset to treatment time and baseline NIHSS. Suspected small vessel strokes were treated somewhat later than those due to large vessel occlusion; however, neither the 24 hour or three month outcomes varied by stroke subtype. The NIH Stroke Scale Score was a confounder for the relationship between onset to treatment time and outcome as the score was higher for tPA-treated patients in the earlier time stratum and higher for placebo patients in the later time stratum. After correction, an odds ratio for a good outcome at 24 hours was 1.71 in the 0 to 90 minute stratum (95% CI 1.09-2.70) and 1.12 in the 90 to 180 minute stratum (95% CI 0.71-1.76). The odds ratios for good outcome at 3 months adjusted for the NIH Stroke Scale Score shows a similar relationship with a value of 2.11 for the 0 to 90 minute stratum (95% CI 1.33-3.35) and an odds ratio of 1.69 in the 90 to 180 minute time stratum (95% CI 1.09-2.62). There was, however, no interaction between onset to treatment time and hemorrhage at 36 hours for symptomatic hemorrhage or all hemorrhages.

We did not conduct a meta-analysis of the effectiveness and safety of thorombolytic therapy for adults with acute ischemic stroke by time from onset to treatment since we identified a meta-analysis published in 2004 that used patient-level data from six RCTs to investigate the interval from onset to treatment using tPA.[195] Findings of this meta-analysis indicated that the sooner the treatment is administered (<90 min) the more beneficial the outcome. Administration beyond 3

hours was found to have some benefit, although with some associated risks. Details pertaining to this patient-level meta analysis are described in the discussion section.

Summary Table 6. Intervention F

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Albers, 2002 US[99]	RCT Parallel	n=61 Inclusion Criteria: Acute IS within 3 hr symptom onset in either part A or B of ATLANTIS; age <79y Comment: Increase risk of symptomatic ICH similar to NINDS trial; small trend towards increased mortality might relate to small sample size and imbalances in baseline prognosis factors	I: Timing of thorombolytic therapy in IS (n=23) C: Control (n=38)	▪ No significant difference in mortality rate (at 3 mo) ▪ Significant increase in rate of ICH in IG ▪ NIHSS (at 3 mo)
Clark, 2000 North America[112]	RCT Parallel	n=142 Inclusion Criteria: Adult acute ischemic stroke, within 6 hr of onset Baseline differences: Significantly more diabetics in CG Comments: Trial stopped early due to safety concerns in the 5-6 hr group	I: tPA 0.9 mg/kg (n=71) C: placebo (n=71)	▪ No differences in primary outcome (proportion with NIHSS improvement of 4 points by 90 d) ▪ No difference in BI at 90 d ▪ mRS better in CG in 90 d ▪ Higher symptomatic ICH in IG in 10 d & higher mortality in IG in 30 d
Clark, 1999 US[67]	RCT Parallel	n=547 Inclusion Criteria: Acute IS with measurable focal neurological deficit of MCA origin; age 18-79y; within 3-5 hr post onset Comments: Negative results apply to patients treated > 3 hr post onset	I: Timing of thorombolytic therapy in IS (n=272) C: Control (n=275)	▪ No significant outcome in mortality (at 3 mo) ▪ No significant difference in functional outcome (BI, mRS, GCS at 3 mo) ▪ Increased ICH rates at 10 d in IG

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Summary Table 6. Intervention F

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Hacke, 1998 Europe, Australia, New Zealanc[107]	RCT Parallel	n=800 Inclusion Criteria: Acute ischemic stroke within 6 hrs of onset, early infarct change on CT less than 33% of the MCA territory Baseline differences: No significant differences between groups	I: rtPA 0.9 mg/kg (n=409) C: Placebo (n=391)	▪ No significant differences in 90 d mortality ▪ No significant differences in proportion with mRS 0 or 1 at 90 d ▪ Increased ICH in IG
Hacke, 1995 Europe [108]	RCT Parallel	n=620 Inclusion Criteria: Acute ischemic stroke, 0-6 hrs, early infarct change on CT less than 33% of the MCA territory Baseline differences: No significant differences between groups Comments: Major protocol violations in 109 patients, 66 in the rtPA group	I: rtPA 1.1 mg/kg (n=313) C: Placebo (n=307)	▪ No significant differences in mortality ▪ No significant in outcome measures (BI, mRS at 90 d)
Haley, 1993 US[113]	RCT Parallel	n=27 Inclusion Criteria: Acute IS causing neurological deficit, age 18-80, within 90 min or 91-180 min post onset Baseline differences: Large imbalance in baseline NIHSS scores in 91-180 min group Comments: Small sample sizes; one person not finishing study in IG with no designation to < 90 m or 91-180 min; benefit to early tx was seen initially but not sustained at 3 months	I: Timing of thorombolytic therapy in IS (n=14) C: Control (n=13)	▪ No significant difference in mortality rates ▪ Significant improvement in functional outcome (at 24h) for NIHSS ▪ No difference in hemorrhage rates

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Summary Table 6 (cont'd). Intervention F

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Marler, 2000 US Part A[55]	RCT Parallel	n=302 Inclusion Criteria: Acute stroke 0-90 min post onset; NIHSS > 4 (based on NINDS tPA study for stroke) Baseline differences: NIHSS score IG > CG Comments: onset to tx time (OTT) significance at ≤10	I: Timing of thrombolytic therapy in IS (n=157) C: Control (n=145)	▪ No difference in mortality rates at 24 hr ▪ OTT interaction at 24 hr favoring treatment (0-90min stratum vs. the 91-180) for functional outcome (composite BI, mRS, NIHSS, GCS)
Marler, 2000 US Part B[55]	RCT Parallel	n=320 Inclusion Criteria: Acute stroke 91-180 min post onset (based on NINDS tPA study for stroke) Baseline differences: NIHSS score CG > IG; more delay in time to tx compare to Part A group Comments: Due to baseline differences in severity of stroke effect of tx may be greater than actual; time to tx: patients with small vessel strokes > patients with cardioembolic or large vessel strokes	I: Timing of thrombolytic therapy in IS (n=153) C: Control (n=167)	▪ No difference in mortality rates at 3 mo; 3 mo functional outcome favoring tx (0-90 min stratum vs. 91-180) for functional outcome (composite BI, mRS, NIHSS, GCS)

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Intervention G: Do Pretreatment CT Scoring Systems Affect the Safety and Efficacy of Thrombolytic Therapy for Acute Ischemic Stroke?

Our searches for interventions examining the effectiveness of pretreatment CT scoring systems for ischemic stroke identified 11 studies. One case-control study,[196] two single prospective cohort studies,[197,198] and six studies whose designs could not be determined,[199-204] were excluded for level of evidence. Two unique studies were included in our final analyses (Summary Table 7).[114,115] Both studies were parallel RCTs and were published in 2001 and 2002, respectively.

Patel et al.[114]examined the frequency and significance of early infarct changes (EICs) on CT scans from the NINDS database. The NINDS trial described previously was a multicenter RCT

carried out from 1991 to 1994 in American centers.[49] The two parts of the trial (A and B) carried identical protocols differing only in the timing of the primary outcome collection with primary outcome being at 24 hours for Part A and 3 months for Part B. Patients with ischemic stroke that could be treated within 3 hours of onset of stroke symptoms were included. Of note, half of these were treated between 0 and 90 minutes of onset. Treatment consisted of tPA 0.9 mg/kg or matching placebo. The CT scan in this trial was used to exclude hemorrhage at the time of the trial. Changes other than hemorrhage were not used to exclude patients. The analysis reported in this paper was carried out in 1994 after conclusion and publication of primary trial results. All CT scans were obtained on third or fourth generation CT scanners with 10 mm thick slices. The coordinating center neuro-radiologist reviewed hard copies of the scans centrally. The site investigator supplied clinical information at the time of the initial treatment. The information included demographics, time since stroke onset, localization, and presumed stroke mechanism along with the component scores of the baseline NIHSS. The EIC's were classified into three groups: 1) loss of gray-white distinction 2) hypodensity, and 3) compression of CSF spaces. Visual inspection was used to classify the changes as being either less than one-third of the MCA territory or greater than one-third of the MCA territory. Of the 624 patients randomized in the NINDS Trial, CT scans of 616 (99%) of the patients were available for review. Early infarct changes were associated with a baseline NIHSS $\rho=0.23$; $p<0.001$) and time from stroke onset ($\rho=0.11$; $p=0.007$). The correlation in both cases was not strong ($\rho=0.23$). Of significant note, the EICs were not correlated with clinical outcomes after adjustment for baseline variables. This included the composite description of the 3-month favorable outcome along with its component measures of mRS Score, NIHSS, Barthel and Glasgow Outcome Score. There is likewise no correlation between the EICs and deterioration at 24 hours, 3-month lesion volume or death within 90 days. Likewise, the presence or absence of the EICs adjusted for baseline NIHSS was not predictive of symptomatic intracranial hemorrhage within 36 hours. These relationships held true whether the EICs composed less than or greater than one third of the MCA territory.

Roberts et al.[205] reported on CT findings and implications from the PROACT II Trial.[115] PROACT II[92] was conducted between 1996 and 1998 and compared treatment of MCA occlusion within 6 hours by IA pro-urokinase coupled with IV heparin and IV heparin alone. The details of this study have been previously described. The current analysis was limited to the 162 patients (108 pro-UK and 54 controlled) who received the treatment. Seventy-five percent of these patients had infarct changes on their baseline CT scan. A neuro-radiologist at the central facility reviewed all CT scans, and baseline CT volume was correlated with clinical variables and outcome.

The baseline CT abnormality volume did not correlate with the baseline NIHSS. There was, however, a modest correlation between baseline CT volume and outcome at 90 days ($r=0.17$, $p=0.05$). Twenty-two of 53 (42%) patients with no CT abnormality at baseline reached a mRS less than or equal to 2 at 90 days. This compared to 2 of 8 (25%) of those with baseline CT changes having a volume of greater than 60 mL. Hemorrhagic infarction was present in 42% of the 108 pro-UK group and 29% of the control group at 24 hours. There was a trend toward increased volume of early CT changes and the presence of infarct. The mean volume in pro-urokinase patients with no bleeding was 11.6 ± 2.7 mL. Those with intracranial hemorrhage had a mean volume of 18.8 ± 3.9 mL while those with hemorrhage and clinical deterioration had a mean early infarct volume of 23.3 ± 8.9 mL.

Summary Table 7. Intervention G

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Patel, 2001 US[114]	RCT Parallel	n=624 Inclusion Criteria: Acute IS < 3 hr (0-90 & 91-180 min) post onset Baseline differences: Reports differences of baseline variables & EIC (early ischemic changes) only Comments: Reports outcomes as baseline CT scan status by tx associated with clinical outcomes and subdivided by EIC > or <1/3 EIC or no EIC; CTs were not used in tx decision	I: Intravenous tPA (n=312) C: Control (n=312)	▪ Early CT changes not correlated with outcome or adverse events
Roberts, 2002 US[115]	RCT Parallel	n=159 Inclusion Criteria: Acute IS of MCA origin within 6 hr of onset; angiography: complete occlusion or contrast penetration with minimal perfusion of M1 or & M2 (based on PROACT (Prolyse in Acute Cerebral Thrombo-embolism) II trial criteria) Baseline differences: NR Comments: Article based on cohort of patients who received randomization & available CTs; no baseline/ follow up information for cohorts is specified	I: IA tPA (n=107) C: Control (n=52)	▪ Baseline CT volume weakly correlated with clinical outcome

RCT = randomized clinical trial; US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Intervention H: Do Pretreatment MRI Scoring Systems Affect the Safety and Efficacy of Thrombolytic Therapy for Acute Ischemic Stroke?

Six studies were identified that addressed the effectiveness of an MRI scoring system for ischemic stroke. One multiple prospective cohort study[101] and one single prospective cohort study[100] were included in our review; they were published in 2002 and 2003, respectively (Summary Table 8). Three non comparative case series reports[206-208] and one case study were excluded for level of evidence.[209]

Suarez and colleagues[101] reported a single-center cohort in which MRI was used to select patients for IA treatment following IV treatment. Patients enrolled had a diagnosis of ischemic stroke whose onset was less than three hours prior to the onset of treatment. The NIH Stroke Scale Score was greater than or equal to 4. An unenhanced CT scan had demonstrated an absence of hemorrhage. The blood pressure was monitored and treated if greater than 180/110. All patients received IV tPA at a dose of 0.6 mg/kg delivered as a 10% bolus over 1 minute with the remainder over 30 minutes. An emergency MRI was conducted subsequently. T1 weighted, T2 weighted, turbo gradient, spin echo, and echo-planar diffusion weighted axial images and axial time-to-peak maps were obtained. They were processed within 6 minutes and interpreted by the neuroradiologist. MRI changes were categorized into four groups: 1) no evidence of infarct 2) evidence of infarct limited to penetrating artery distributions 3) diffusion imaging (DWI) and perfusion-weighted imaging (PWI) mismatches suggesting infarct involving cortical and subcortical areas, or 4) PWI/DWI matched abnormalities suggesting acute infarction involving cortical and subcortical areas. Patients who had no signs of infarct on the MRI or infarcts involving only perforating artery distributions were not treated further. All others had urgent cerebral angiography. If occlusion was demonstrated on the angiography, patients were treated with either urokinase or tPA. This protocol initially started using urokinase, however, switched to tPA after FDA approval of IA tPA for acute ischemic stroke. The urokinase protocol involved an initial dose of 250,000 units repeated up to three times if the vessel did not recanalize. The tPA protocol involved 5 mg repeated until maximum dose of 0.9 mg/kg was achieved over the vessel recanalized.

A total of 2,180 patients were seen at the center during this period of which 554 presented within 3 hours. Forty-five patients met eligibility criteria including consent for this protocol and were considered for angiography. Of these, 21 patients were treated solely with intravenously administered tPA. Seven of these had normal MRI findings while four had evidence of small subcortical defects and two had complete ICA occlusions. One patient exhibited complete improvement prior to angiography, and two patients had normal angiographic results after abnormal MRI results. The mean delay added by MRI imaging was 17 minutes with mean time to complete IA treatment of 282 ± 41 minutes in the urokinase group and 290 ± 38 in the tPA group. For the 24 patients who received IA tPA, the majority recanalized, 18/24. The pre-specified criterion for good clinical outcome was a Barthel Score of greater than or equal to 95 at 3 months. This was achieved by 92% of those in the IA urokinase group (12/13), 64% in the IA tPA group (7/11), and 66% of those in the IV treatment group (14/21).

Hermier et al.[100] reported on the use of MRI characteristics employed prospectively to examine the predictive value of early clinical and MR parameters on recanalization in thrombolytic treatment and late infarct volume. Patients were accrued between 2001 and 2002 at a single center in France. Patients with an ischemic stroke within the carotid territory who could receive MRI scanning and IV tPA within 6 hours were included. An NIHSS greater than 4 and an absence of bleeding on unenhanced CT were required. A baseline MRI scan including time-of-flight MR angiograpy, and DWI/PWI, was obtained. Patients with lacunar syndromes determined either clinically or after MRI, were excluded along with hemodynamically relevant stenoses of the extracranial arteries, which might affect time-to-peak analysis. A neuroradiologist who was unaware of the clinical data carried out interpretation of the MRI scan. All patients received IV tPA 0.8 mg/kg. Of 510 patients diagnosed with a stroke, 61 had stroke in the carotid artery and could receive the MRI within 6 hours. Of these patients, 32 met

inclusion criteria and received a baseline MRI scan; three of these patients were excluded since their baseline scans were obscured by a motion artifact.

The correlation between the NIH Stroke Scale Score and recanalization at day 1 was demonstrated with a NIH Stroke Scale Score of less than 15 correlating with canalization in the early time frame (p=0.046). The time-to-peak within the DWI lesion on day 0 was likewise correlated with early recanalization. Thirteen of 15 patients (93%) whose baseline time-to-peak was less than or equal to 36.9 milliseconds recanalized within the first day versus 5 of 15 patients (35.7%) whose time-to-peak was greater than 36.9 milliseconds. The NIH Stroke Scale Score and baseline time-to-peak value were the most powerful predictors of recanalization on multi-variate analysis at day 0. Both the day 0 DWI lesion volume and day one recanalization predicted the 60-day infarct volume. Of note, the extent of day 0 DWI/PWI mismatch had non-predictive value for early recanalization. Recanalization was correlated with a better clinical outcome at day 60.

Summary Table 8. Intervention H

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Hermier, 2003 France[100]	Single Prospective Cohort	n=28 Population Characteristics: Acute IS, with pre-tx & within 6 hr MRI; NIHSS > 4 & no contraindication to tPA tx; with recanalization on MRI (IG) or persistent occlusion on MRI (CG) Comments: Small sample size; assessment of perfusion based on only seven perfusion weighted image (PWI) slices which might have caused underestimation of the volume of abnormality	Observational study correlating outcome with measured parameters	▪ Recanalization correlated with clinical outcome at 60 d ▪ Initial DWI lesion volume & recanalization at d 1 predicted 60 d infarct volume
Suarez, 2002 US[101]	Multiple Prospective Cohort	n=45 Population Characteristics: Acute IS < 3hr post symptom onset; no improvement on clinical sign; no ICH on CT; age 18-80; NIHSS score ≥ 4 Comments: Study was limited with small sample size, lack of CG, & use of two different thrombolytic agents; tx dose of tPA lower than standard approved by Food & Drug Administration; good clinical outcomes (BI) was reported at 3 mo post tx for survivors	I: Combined intravenous/intraarterial thrombolysis (n=45)	▪ Symptomatic intracranial hemorrhage 4.4% ▪ Mortality 7/45 (16%)

US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Intervention I: Do CT Perfusion/Angiography Affect the Safety and Efficacy of Thrombolytic Therapy for Acute Ischemic Stroke?

Three studies (four publications) examining CT perfusion/angiography for ischemic stroke were identified.[102,116,210,211] One potentially relevant trial[210,211] was published in abstract form and the authors were contacted to determine if subsequent articles were published. These were excluded following full text screening. Study design could not be determined in two publications and were excluded for level of evidence.[212,213] One single retrospective cohort study[102] and one case-control study[116] were included in our review (Summary Table 9). They were published in 2001 and 2004, respectively.

Agarwal and colleagues reported on the significance of the hyperdense MCA sign in selecting patients for IA versus intravenous thrombolysis in a cohort of patients collected at a single American center between 1996 and 2001.[116] Consecutive patients presenting at the center with acute ischemic stroke were considered; those patients who arrived within 3 hours of symptom onset and had no contraindications to tPA, were treated with 0.9 mg/kg following the NINDS protocol. Patients with a contraindication to intravenous tPA or presenting within 3 to 6 hours underwent IA treatment. In these individuals, a #5 French sheath was placed in the right common femoral artery followed by selective catheterization of the occluded cerebral artery. The guidewire was used to provide mechanical disruption followed by the administration of 14 to 20 mg of tPA by an infusion microcatheter. The total dosage was determined by the presence of recanalization or upon reaching the maximum dose of 20 mg. All patients received evaluation for MCA hyperdensity and other changes of early infarction. A hyperdense MCA was defined by: spontaneous visibility of the whole horizontal part of the MCA; density of the MCA higher than that of the surrounding brain; disappearance on bone windows; unilaterality; and, absence of hemorrhage. The M2 dot sign was defined as hyperdensity of an arterial structure seen as a dot in the sylvian fissure. Obscuration of the lentiform nucleus, loss of the insular ribbon, and hemispheric effacement were also assessed. A 24-hour neurologic improvement, defined as a 4-point NIHSS Score improvement from baseline, was evaluated.

During the course of the study, 66 patients were treated with intravenous tPA and 17 by IA tPA. The presence of the hyperdense MCA sign did not predict neurologic recovery in the IA treated patients with three of eight patients who had the sign achieving 24-hour recovery as defined, along with three of nine patients who did not have the sign. The hyperdense MCA sign, however, did predict recovery, with two of 15 patients having the hyperdense MCA sign achieving 24-hour recovery; conversely, 30 of 51 patients lacking the sign achieved 24-hour neurologic recovery ($p=0.005$). The M2 dot sign, loss of insular ribbon, obscuration of lenticular nuclei, and sulcal effacement, were not predictive of recovery with either intravenous or IA treatment.

The hyperdense MCA sign was associated with a greater probability of recovery with IA than intravenous treatment (37% versus 13%). This observational data[116] suggests that this sign may be used as a tool to triage patients between intravenous and IA treatment. There is a probability that proximal large vessel occlusion may be associated with worse outcomes intravenously. This observation will require testing in a prospective study.

Kirpatrick and colleagues[102] reported on a retrospective cohort of patients from a single center between 1997 and 2000. These were selected on the basis of an electronic record search seeking all patients within the period of enrollment who would have had a CT scan, CT angiogram and Xenon CT cerebral blood flow within 24 hours of a stroke. The clinical team ordered the studies at the time of the patient's presentation. Primary intent of the study was to see whether abnormalities on these studies or the NIH Stroke Scale were predictive of infarct on the follow-up CT scan. The NIH Stroke Scale was obtained from the record or calculated from the neurologic examination in the record. The CT scan was reviewed by the investigators in a blinded fashion. The CT angiogram was coded based on the report contained within the record. All CT angiograms were performed on a GE Lightspeed scanner with axial helical images obtained from the level of C6 through the circle of Willis with 3 mm collimation. The CTA was defined as patent if there was no report of occluded or stenotic vessels. It was considered

occluded if the ICA or MCA on the symptomatic side were reported to be occluded or heavily stenosed. The Xenon CT cerebral flow image was obtained at four levels and mean CBF values were calculated at 20 standardized cortical regions of interest. The scan level containing the lowest average flow in the MCA territory on the symptomatic side was used. This flow was categorized as normal (greater than or equal to 30 mL/100 g/minute), potentially reversible (7 to 29 mL/100 g/minute) or irreversible (less than 7 mL/100 g/minute). The latter two categories were combined due to the small number of patients for statistical analysis. The groups were further subdivided into those examined within six hours of stroke onset and those greater than six hours. The latter group was too small to draw any conclusions. In the group examined prior to six hours (n=31), the NIH Stroke Scale Score was not predictive of infarct on the follow-up CT scan. Normal cerebral blood flow on the Xenon CT resulted in a rate of infarct of 8% (1/13), while abnormal Xenon CT blood flow resulted in a rate of infarct of 55% (6/11). This difference was statistically significant (p=0.023). A CT angiogram showing patent vessels was associated with a rate of infarct of 7% (1/14 patients) while CT angiogram showing occlusion had an infarct rate of 60% (6/10). This too was statistically significant (p=0.008).

Summary Table 9. Intervention I

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Agarwal, 2004 US[116]	Case Control	n=83 Inclusion Criteria: Acute IS, according to TOAST criteria; < 3 hrs post onset (IG) or 3-6 hrs post onset & patients excluded for IV tPA based on NINDS criteria (CG) Baseline differences: NR Comments: Significantly shorter time to tx in IG	I: Intravenous tPA (n=66) C: Intraarterial tPA (n=17)	▪ No correlation with HCMAS and outcome for CG ▪ HCMAS associated with poorer neurologic improvement at 24h in IG
Kilpatrick, 2001 US[102]	Single Retrospective Cohort	n=51 Population Characteristics: Acute hemispheric IS within 24 hrs post symptom onset, undergone CT, CT angiography & xenon-enhanced CT, cerebral blood flow; NIHSS score 1-26 Comments: Small sample size; possible selection bias	Observational study examining the prediction of (n=51)	▪ Decreased CBF associated with higher rate of infarction ▪ CT angiogram occlusion associated with higher infarction

US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Intervention J: Are Community Education Programs Effective in Reducing Stroke-Related Disability and Mortality?

One controlled clinical trial,[103] six before-after studies,[214-219] and one study for which study design could not be determined,[220] investigated the use of community education programs for acute stroke. Subsequently, seven studies were excluded for level of evidence.[214-220] Only one study[103] was included for our review (Summary Table 10). This study was a controlled clinical trial and was published in 2003. The before-after studies did not address relevant clinical outcomes and thus we were unable to extract data from these studies. We did however summarize the studies, including population characteristics and limitations in the Appendix. (Appendix E)

Prior to FDA approval of thrombolytic treatment, acute stroke was not perceived as an emergent reason to present to a healthcare facility. Educational programs for the community and healthcare professionals involved in care of patients with acute stroke were deemed essential, as thrombolytic therapy must be urgently administered in order to be beneficial.

The TLL Temple Foundation Stroke Project was established after approval of thrombolytic therapy by the FDA, with the goal to increase utilization of this therapy in a non-urban community in East Texas. Results of the first and second phases of the study have been published[221]—phase 1 reported on baseline data in the intervention community and the control community and the development of the intervention; phase 2 included an evaluation of the intervention.

Morgenstern et al. reported on the third phase of the TLL Temple Foundation Stroke Project—a quasi-experimental comparison between two communities to determine if the beneficial effect of the Community and Professional Intervention would be sustained after the active intervention had been completed.[103] In this report, comparisons are made with the other phases of the project in a before-after design. The financial sponsors of this project mandated that a specific community receive the intervention, and that another, comparable community be chosen by the project investigator. The intervention and its development were published in a companion publication.[221] In summary, the intervention was developed based on the process of Intervention Mapping to create a multi-level program that delivered a community communication campaign combined with professional development and organisation change to increase access to stroke therapy in rural east Texas. Target behaviors of lay community (the "at-risk group"), EMS, ED physicians, neurologists, and community primary care providers were identified, and educational and infrastructure changes were given. For example, to target community members, public service announcements were created using local role models, volunteers were trained to take the message to community groups, and educational pamphlets were distributed. Changes made to EMS included assigning a higher priority for the transport of acute stroke patients, development of protocols, and reinforcement and use of mock stroke codes were performed. To target physicians, changes included providing continuing medical education provided, the use of mock stroke codes, and the distribution of newsletters.

Active surveillance by fellowship stroke-trained neurologists, was used to capture all hospitalized stroke cases in the 10 hospitals (five from each community) using a method developed by WHO in the Monica Study.[222]

In this third phase of the study, 2,184 patients were screened, and 238 validated cases were documented. Baseline demographics of patients from the two communities were different. Patients from the control community had a higher prevalence of co-morbid illnesses compared with the intervention group community: hypertension (87.5% vs. 75.4%); diabetes (48.2% vs. 27.1%); CAD (56.9% vs. 31.5%); AF (68.4% vs. 10.9%); and, previous stroke (65.2% vs. 44.1%). More patients in the control community had a neurological consultation compared with the intervention community (59.1% vs. 45.0%).

The primary outcome was the proportion of patients treated with IV alteplase. This included, nine out of 13 eligible patients (69.2%) in the intervention community, compared with only one of 5 eligible patients (20%) in the control community. The secondary outcome was the proportion of patients who presented to the hospital within 2 hours of symptom onset. There was no significant difference between the two communities—i.e., 28.6% of patients from the intervention community and 22.6% of patients in the control community.

A comparison in both communities over the three phases of this project was reported for internal hospital delay and physician reluctance to utilize tPA in acute stroke. In the intervention community, there was a significant reduction in the proportion of patients who experienced internal hospital delay and a significant reduction in physician reluctance to utilize tPA in acute stroke. In the control community, there was a similar reduction in hospital delay but no change in physician reluctance to utilize tPA over the three phases of this project.

Summary Table 10. Intervention J

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Morgenstern, 2003 US[103]	Controlled Clinical Trial	n=1427 (for all 3 phases); phase 3 only: n=238 Inclusion Criteria: County residents experience of cerebrovascular event; IV tPA inclusion according to NINDS criteria Comments: Study demonstrates a sustained benefit from educational intervention, with possibility of physician professional intervention being the most or only successful part of the intervention	I: Community education program for acute stroke (n=748/ phase 3: n=130) C: Control (n=679/ phase 3: n=108)	▪ 11.2% of ischemic stroke treated with tPA vs. 2.2% ▪ Improvement in frequency of IV tPA tx in eligible candidates

US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Intervention K: Are Designated Centers Effective in Reducing Stroke-Related Disability and Mortality?

Initially, no studies meeting eligibility criteria for investigating the use of designated centers as defined by the Brain Attack Coalition were identified by our searches. However, two studies[104,105] were included since they provided valuable end points (numbers treated and time to treatment). Both studies were single prospective cohort designs and were published between 2000 and 2003 (Summary Table 11).

It has been hypothesized that to increase utilization of thrombolytics, a dedicated stroke center strategy should be developed.[5] The studies we included were felt to most closely resemble the model of a designated stroke center as defined by the Brain Attack Coalition and detailed by Alberts et al. (2000) in their recommendations for the establishment of primary stroke centers.[5]

Hill et al.[104] reported on building a "brain attack" team to administer thrombolytic therapy to patients with acute stroke and on their initial experience with IV-administered thrombolytics. Although thrombolytic therapy was approved for use in Canada in 1999 (the FDA approved its use in the U.S. in 1996), the Calgary Regional Stroke Program received special permission from the local health authority and began a program of open-label thrombolytic therapy for stroke in 1996 following FDA approval for its use in the U.S. The project was initially approved as a pilot study; after 20 patients, an audit was performed to assess safety and complication concerns. The model of care was organized around five essential elements of acute stroke care (all beginning with the letter "R"): Recognition, Reaction, Response, Reveal, and Reperfusion. The major changes that were instituted to achieve success of this program was the funding of a "blocked bed" on the stroke unit i.e., a bed that was always available for a patient to receive thrombolytic therapy enabling rapid removal of patients with acute stroke from the ED. In addition, a campaign was launched to educate the public to increase awareness and "recognition" of stroke symptoms. EMS were asked to change their dispatch protocols to decrease "response" times by elevating acute stroke to a priority one transfer where all patients with stroke-onset symptoms less than 3 hours were preferentially transferred to the stroke center, bypassing other hospitals. The stroke center was contacted by EMS, and the stroke team contacted on patient's arrival to ED thus decreasing the "reveal" time. The ED staff treated stroke as a life-threatening situation, performed a preliminary assessment, and urgently arranged for CT scanning to decrease the time to "reperfusion".

The initial audit of 20 patients revealed no safety concerns.[104] From the inception of the stroke program through to Jan 31, 1999, 69 patients were treated with IV-administered thrombolytics. A 1-year audit demonstrated that 6% of all patients admitted with acute stroke were treated with thrombolytics. Outcome data, reported in a separate publication,[223] compared favorably with data reported in published RCTs, with the exception that when patients were treated beyond the 3-hour window, 25% had a symptomatic hemorrhage with 83% of these patients having died by the 90-day follow-up.

Hill et al.[104] reported that EMS had treatment times equal to or less than target times recommended by the NINDS stroke study group,[224] with a mean time from symptom onset to ED arrival of 55.8 minutes (range 15-125 minutes). Once the patient arrived at the ED, a mean time

of 46.1 minutes (range 5-130 minutes) was required to obtain a CT scan and a further mean time of 55.6 minutes (range 20-315 minutes) was required for initiation of thrombolytic treatment. Treatment times improved significantly over the study period—mean treatment time for the first half of the study period was 63.3 minutes compared with 48.6 minutes for the second half of the study. ED to CT and ED to treatment times did not significantly change. Overall symptom onset to treatment time was significantly decreased from a mean of 167.8 minutes to 147.4 minutes.[104]

Hill et al.[104] concluded that if the public can be taught to recognize the symptoms of stroke and react by calling EMS, EMS will promptly get the patient to the hospital. The authors were sobered by the fact that the improvement in time gain overall, was due primarily to getting patients to the hospital faster.

A 4-month pilot study was started at Suburban Hospital in Bethesda MD to establish a stroke center for the region.[105] A stroke critical care pathway was developed which incorporated EMS policies, immediate notification of the stroke team, initiation of urgent diagnostic tests, and medical management for thrombolytics. Community education (i.e., lectures emphasizing the symptoms of stroke and need for rapid response by activation of EMS and risk assessment screenings) targeting local community centers, particularly those with senior citizen populations, was provided by the stroke team. Stroke education was provided to ED personnel, hospital personnel, diagnostic imaging, and laboratory staff as well as regional EMS and the local community.

On January 3, 2000, around-the-clock coverage was instituted for acute stroke.[105] The stroke-care critical care pathway mandated contacting the stroke team for any patient presenting with a suspected new stroke and persistent deficit <6 hours in duration. Data was collected prospectively until December 31, 2001 for all patients assessed by the stroke team including demographic data, presentation times, treatment times, reasons for non-treatment, radiological times and findings, stroke scale results (NIHSS, mRS), and disposition. Measured time intervals to action (in minutes) were computed as a running 2-month average.[105] Results were compared with benchmarks from the Standard Treatment with Alteplase to Reverse Stroke Study (STARS).[225]

A total of 511 patients were admitted to the hospital with a diagnosis of suspected ischemic stroke; 420 patients had the diagnosis confirmed and 271 arrived within 3 hours of symptom onset.[105] Over the 2-year period the following times decreased: time from patient arrival to paging of the stroke team (median of 24 min to 10 min); time from receiving the stroke-team page to arrival of the stroke team (median of 28 min to 6 min); and, time of triage to time of CT (median of 52 min to 42 minutes). The overall median time to treatment from onset was 134 minutes, and the median door-to-needle time was 88 minutes.[105]

During the 4-month pilot study, four of 117 patients with ischemic stroke were treated with thrombolytics (3.4%).[105] Of the 420 patients diagnosed with suspected ischemic stroke over the 2-year study period, there were 44 patients treated with thrombolytics—10.5% of the total and 16.2% of those arriving to hospital within 3 hours of the onset of symptoms.[105] Clinical outcomes and time to treatment were similar to that reported by STARS.[225]

This study demonstrated that a coordinated stroke strategy and development of a stroke center led to a decrease in treatment and investigation times over the investigation phase in addition to increasing the proportion of patients who received thrombolytics.[105]

Lattimore and colleagues reported the experience of establishing an acute stroke program at a Maryland hospital.[105] The community education program associated with this effort consisted of multiple onsite programs with screening efforts, lectures and engagement of local media that were coupled with an intense reorganisation of ED protocols and designation of an acute stroke response time. Delay time prior to the intervention was not reported but an increase in the treated proportion, from 1.5% prior to the intervention to 10.5% during the subsequent 2 years, was noted. No comment was made regarding the relative contributions of the elements of the intervention to the observed outcome. Thus, the relative contribution of the educational effort cannot be separated from the overall effect.

Summary Table 11. Intervention K

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Hill, 2000 Canada[104]	Single Prospective Cohort	Inclusion criteria: Acute IS, treated within 3 hrs of symptom onset	Observational study describing development of designated centers for acute stroke	▪ 6% of IS treated within the 1st y of program inception (n = 69)
Lattimore, 2003 US[105]	Pre-Post	Inclusion criteria: Acute IS with persistent neurological deficits, all inclusion criteria based on NINDS & guidelines from a Special Writing Group of the American Heart Association	I: Use of designated centers for acute stroke	▪ Establishment of stroke center correlated with S increase in proportion of IS treated (1.5% to 10.5%)

US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Intervention L: Are ED Protocols for the Management of Acute Stroke Effective in Reducing Disability and Mortality?

After the publication of NINDS,[49] proponents have widely advocated for the implementation of "stroke teams" to increase the proportion of patients who are eligible to receive thrombolytic therapy and increase utilization of thrombolytic therapy in this population.[49]

From our search we identified one case-control study,[226] two single prospective cohort studies,[118] two single retrospective cohort studies,[106,117] two non-comparative case series studies,[227,228] and two studies whose design could not be determined.[229,230] The case-control and non-comparative studies were excluded for level of evidence. Four studies[106,117,118] examining the effect of ED protocols for management of acute stroke met our eligibility criteria and were included in our final analyses (Summary Table 12). These studies were published between 1999 and 2003.

Smith et al.[106] proposed an ED model for two main reasons. First, EDs were already staffed for rapid assessment, and second, an ED model was already used for administering thrombolytics for acute myocardial infarction in many centers. Smith and colleagues' ED model included guidelines and checklists to evaluate exclusion and inclusion criteria for treatment with thrombolytics, an informed consent package, treatment guidelines including dosing charts, and post-treatment ICU order sets. Prior to implementation, educational efforts using lectures, small group sessions, and written material were directed at the ED physicians, nursing and ancillary staff and other services including Radiology, Neurology, and the ICU. All ED physicians had access to their local neurologist, and at the same time a regional stroke team was also in development.

They performed a retrospective analysis of patients included in their ED model in four teaching hospitals in Michigan. Pharmacy records were used to identify patients treated with thrombolytics and the information was cross-referenced with medical record searches using diagnosis-related group codes used to identify all patients with acute stroke and thrombolytic use. A study physician reviewed each identified record to abstract patient demographics, medical and social history, physical exam findings, complications, length of stay, and stroke severity using the NIHSS. The physician reviewer estimated within 5-point ranges the NIHSS based on documented physical examination in the medical record prior to treatment if the NIHSS was not documented in the medical record. The primary outcome was length of hospital stay, as well as whether the patient was ICH symptomatic or not, pre-hospital time to ED presentation, and ED time data.

Over the study period, 37 patients received thrombolytic therapy. The average time from onset of symptoms to ED arrival was 64 minutes for patients arriving by EMS and 84 minutes for those arriving by car. This data was given for only two of the hospitals that provided care for 24 of the patients. Times for care in the ED were available for 34 of the 37 patients. Thrombolytic therapy began an average of 97 minutes after arrival in the ED and 166 minutes after stroke onset. Neurology consultation was provided for 23 of the 37 patients (nine in person and 14 by telephone). Treatment protocol violations were identified in seven patients, all relating to administration of thrombolytic therapy after the 180-minute time window. Four of the 37 patients developed a symptomatic hemorrhage within 36 hours after treatment but none of these patients were treated outside the 180-minute time window. Neurological outcomes in the 35 survivors at the time of discharge were normal for four patients, improved for 16 patients, unchanged for 10 patients, and worse for five patients. Fifteen patients were discharged home and 15 to a rehabilitation facility.

Time intervals used in the ED model compared favorably to times reported in publications of dedicated stroke teams.[231] ED physicians consulted a neurologist in the majority of cases but

often only a telephone discussion was required to support facilitating the timeliness of administering treatment.

Akins et al. reported on a study that also evaluated an ED-based protocol for delivering thrombolytic therapy with transfer of patient care to a neurological service when feasible.[117] This group established a prospective stroke registry of patients treated with thrombolytics at five community hospitals within the Mercy Healthcare system of Sacramento. Forty-six consecutive patients who received thrombolytic therapy are reported in this study. The local ED physicians developed their own approach to thrombolytic therapy in collaboration with neurologists and radiologists. Clinical information was abstracted from patient records using a standardized form, and clinical outcomes included the mRS score obtained by telephone contact with the patient or family 3-months after treatment. Complete data was obtained on only 43 patients. The dependent variable for analysis was treatment initiation by an ED physician (n=23 patients) or a neurologist (n=20 patients).

There were no differences between the two groups in terms of age, baseline stroke severity (NIHSS), ED presentation to thrombolytic therapy, recovery to normal function, mortality, or symptomatic hemorrhage rates. A trend was detected for a shorter time interval from CT scan to treatment by a neurologist. This was felt to be secondary to the ability of the neurologist to interpret the CT scans.

Initially, during the first year of the protocol, there were more protocol deviations. Thus, a local education program was given to ED staff and local neurologists. As well, nurse stroke-specialist support was implemented in all five hospitals. Seven protocol deviations occurred before the education endeavor compared with only one after the education program was provided. It was not explicitly reported who made the protocol deviations but it is stated in the discussion that it was not surprising that ED physicians would make errors in the dosing of thrombolytics, as it was a markedly different dose than they were conditioned to use for patients with acute myocardial infarction. Details regarding the education program and data collection were not well presented; hence, an independent assessment of the effectiveness of the program was not feasible.

Jahnke et al. reported on their experience with ED stroke teams and acute stroke pathways, over a 2-year period.[118] This group recognized a problem in achieving target times for thrombolytic treatment after a retrospective review that determined that the majority of potential candidates for treatment arrived in the ED more than 2 hours from symptom onset. They developed a stroke team and implemented a written stroke pathway. Prior to implementation, the emergency personnel were educated using group sessions and posters displayed in the ED. The pathway included a standardized set of orders and instructions for the management of acute ischemic stroke. Listed on the pathway were universal stroke symptoms to help staff recognize eligible patients. The pathway gave consideration to the time of stroke onset to determine potential eligibility of the patient for thrombolytic therapy, and urgent activation of the stroke team would occur for patients who presented less than 6 hours from onset of symptoms or non-urgent calls for patients with transient ischemic stroke or symptom with onset >6 hours. The ED physician assessed all patients, and a member of the stroke team would assess and calculate the NIHSS. Documentation of times was performed to allow rating of performance of the stroke team.

Implementation of the pathway identified a number of strategic changes that needed to perform to ensure success. This included identification of two levels of stroke team referral, urgent and non-urgent patients. Also, a major delay identified was time to obtain a CT scan; the CT scanner was geographically distant from the ED and this led to placement of a CT scan in the ED. Another delay identified was time to obtain laboratory test results. Again the laboratory was geographically distant and point of service laboratory equipment was obtained for the ED.

Over the 2-year period, 71 patients were eligible for thrombolytic therapy; 65 patients received treatment and six patients declined. Of the patients who received treatment, one patient died, two required nursing home level of care, 25 were transferred to rehabilitation and 37 were discharged home. Comparing the first year to the second year, there were significant decreases in the following time intervals. First, time from presentation in the ED to ED physician assessment decreased from an average of 33 minutes to 7 minutes. Second, time from presentation to CT scan order decreased from an average of 38 minutes to 7 minutes. Lastly, time from presentation in the ED to completion of the CT scan decreased from an average of 88 minutes to 44 minutes. Compliance for initiating the stroke pathway increased from 40% to 97% of eligible patients, and "door-to-needle" time for the administration of thrombolytic therapy decreased from an average of 111 minutes to 77 minutes. This group still hopes to achieve the NINDS 60 minute goal.

Summary Table 12: Intervention L

Study Identification	Study Design	Population Characteristics	Intervention (I) /Comparator (C)	Relevant Outcomes
Akins, 2000 US[232]	Single Retrospective Cohort	Inclusion criteria: Consecutive acute IS treated with IV tPA according to NINDS protocol treated by emergency room physician or neurologist	Observational study examining ED physician's ability to initiate thrombolysis	▪ Protocol deviations higher for ED physicians compared to neurologists ▪ Number of patients treated n=43
Jahnke, 2003 US[118]	Single Prospective Cohort	Inclusion criteria: Acute stroke with mild to severe neurological deficits	Observational study examining ED protocol	▪ Number of patients treated n=65 ▪ Door-to-needle time decreased following implementation of the protocol
Smith, 1999 US[106]	Single Retrospective Cohort	Inclusion criteria: Acute IS treated with tPA, presented to ED 64 (29) min post onset	Observational study examining the ability of ED physicians to treat thrombolysis	▪ Of 37 patients treated, door-to-needle time was 97± 35 min

US = United States; NR = not reported; n = number of participants; y = year; mo = month; d = day; hr = hour; min = minutes; s = second; IS = ischemic stroke; ICH = intracranial hemorrhage; MCA = middle cerebral artery; IG = intervention group; CG = control group; tx = treatment; IV = intravenous; IA = intra arterial; (r)tPA = (recombinant) tissue plasminogen activator; MRI = magnetic resonance imaging; CT = computed tomography; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; BI = Barthel Index

Results of Meta-Analyses

Meta-analyses could only be performed on two of the interventions examined (Intervention A and Intervention C).

Intervention A: Does Surgery Impact the Outcome in Patients with Acute Intracerebral Hematoma?

Death and Disability: The meta-analysis for the mRS included four eligible studies (Figure 2).[88,89,119,120] Two studies[87,121] were excluded from our disability analysis (mRS score 0 to 1) because data could not be extracted. Juvela et al.[121] reported morbidity of survivors at 6 months after hemorrhage for both groups using an independently derived scale which describes patients as either independent (minimally or moderately disabled) or dependant (severely disabled or vegetative). Morgenstern et al.[87] reported median values (Barthel <61) at 6 months that identified patients with either poor outcome or death. The four trials had a total of 246 subjects (range, n=20 to n=100). Note that the Batjer study[120] made no contribution to the pooled estimate since in both groups all patients experienced death or severe disability.

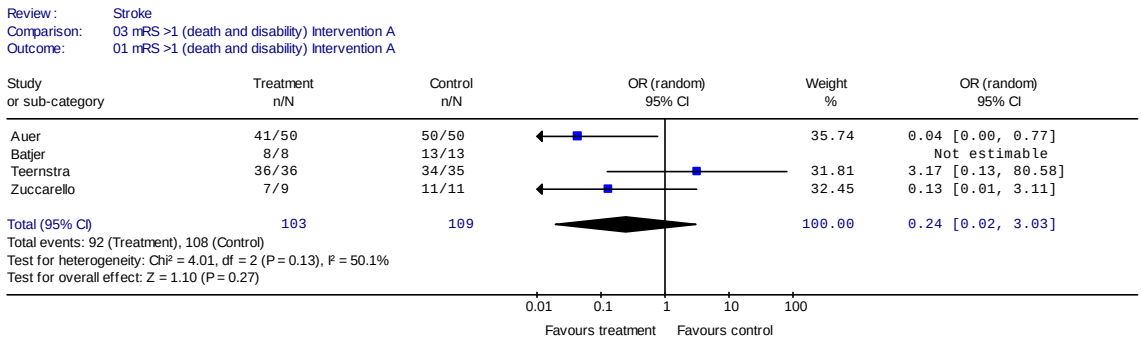

Figure 2. Meta-analysis of the impact of surgery on death and disability in patients with acute intracerebral hematoma.

Note that of the three studies that contributed to the above meta-analysis, there was substantial heterogeneity, therefore, the random effects pooled estimate (and associated confidence interval) should be interpreted with caution.

Death: The meta-analysis for death outcomes included six eligible studies (Figure 3).[87-89,120,121,121] Summary Table 1 includes a description of eligible trials. All studies examined the effectiveness of surgical intervention compared with standard or usual care. The six studies had a total of 298 participants (range, n=20 to n=100). Follow-up interval for studies was 90 days for all studies.

Two reports examining surgical intervention for surgical intervention for intracerebral hemorrhage (a meta-analysis published in 2002[233] and randomized trial published in 2005[122]

were also identified. The meta-analysis included two studies which were not captured by our searches. One by McKissock et al. was published prior to our search date of 1964. The second, by Chen (1992) was a non-English language citation, and hence, was excluded by our search strategy. The Surgical Trial in Intracerebral Haemorrhage (STICH)[122] was published beyond our search date, but was identified by a reviewer. With regards to the Chen 1992 trial, we were able to extract enough mortality data from this meta-analysis[233] to use as a sensitivity check in our current meta-analysis, as well as from the STICH trial.[122] (Figure 4). We could not extract data from the STICH trial for death and disability outcomes (mRS) because they used a prognosis-based modified Rankin index which did not permit us to recover the modified Rankin index.

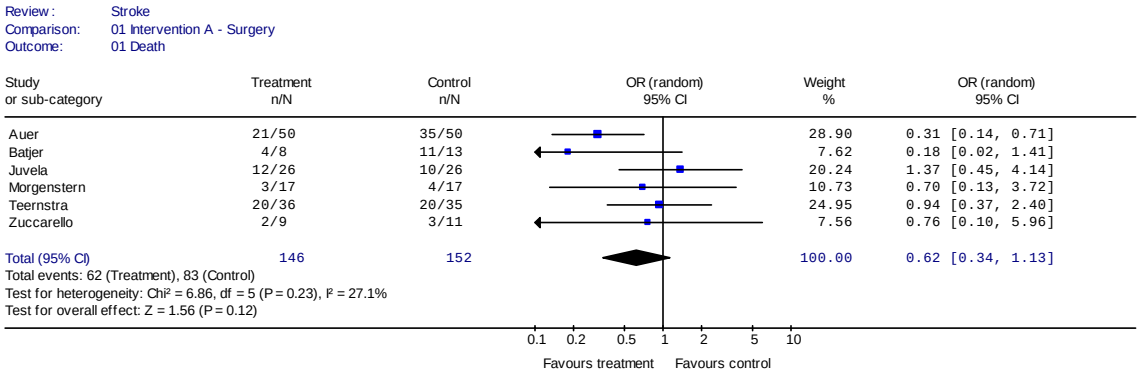

Figure 3. Meta-analysis of the impact of surgery on death in patients with acute intracerebral hematoma.

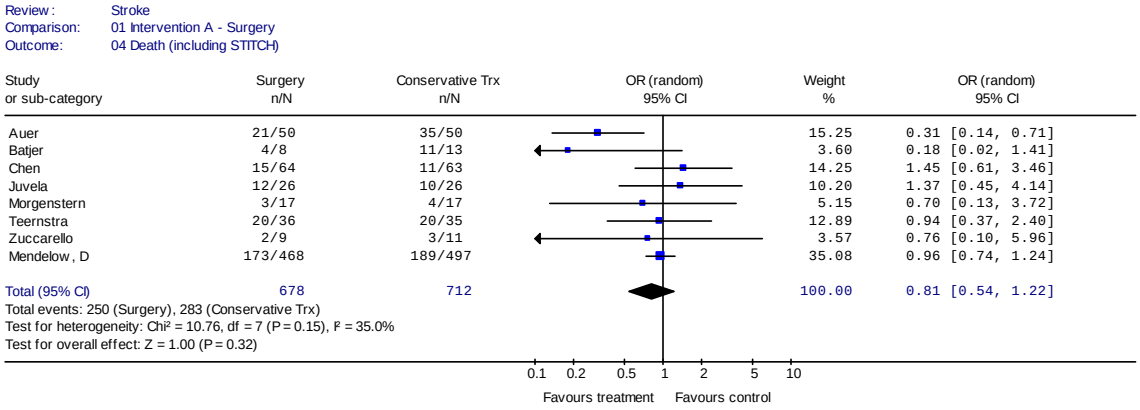

Figure 4. Meta-analysis of the impact of surgery on death in patients with acute intracerebral hematoma including data from the Chen RCT (data extracted from a meta-analysis published in 2002)[51] and STICH[122] trial.

Regardless of whether the Chen study is included, the pooled estimate is not statistically significant. There was, however, a moderate degree of heterogeneity in study outcomes. Note that only the study by Auer[119] showed a statistically significant benefit from surgery.

Intervention C: Does IA Thrombolysis Reduce Stroke-Related Mortality and Disability in Adults with Acute Stroke?

Death and disability. Two studies examining the use of IA tPA for acute ischemic stroke were included in our meta-analysis (Figure 5).[92,110] The two trials included 220 subjects. Note that in this case, there is no detectable statistical heterogeneity, and the random effects model provides identical results to a fixed effects model.

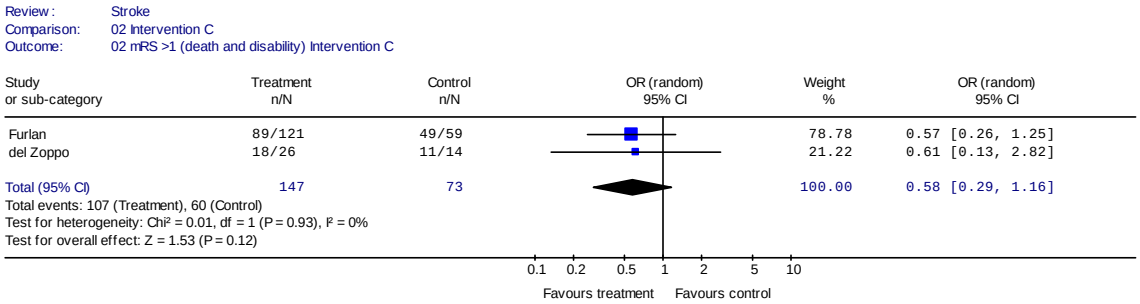

Figure 5. Meta-analysis of the impact of IA thrombolysis on death and disability in patients with acute ischemic stroke.

Death: The meta-analysis for death outcomes associated with the use of IA tPA for acute ischemic stroke included two studies (Figure 6).[92,110] The two trials included 220 subjects. Note that in this case, there is no detectable statistical heterogeneity, and the random effects model provides identical results to a fixed effects model.

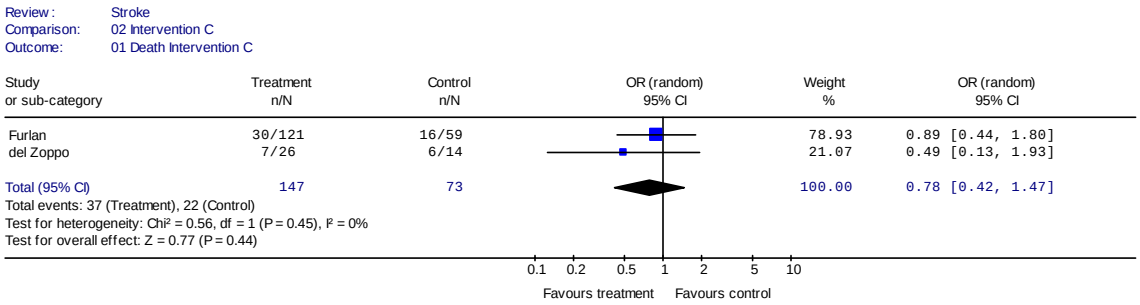

Figure 6. Meta-analysis of the impact of IA tPA on death in patients with acute ischemic stroke.

Statistical significance of pooled results. Neither of the pooled estimates was statistically significant. Note, however, that the wide confidence intervals of the pooled estimates do not rule-out the possibility of substantial benefit from IA thrombolytic therapy.

Chapter 4. Discussion

Studies of Treatment of ICH

The meta-analysis performed for the surgical trials, for both death, and death and disability, showed heterogeneity within the trials. This may be the consequence of different surgical techniques used in the trials. The confidence interval associated with a pooled effect estimate for both endpoints is large and does not preclude a clinically significant treatment effect from surgical intervention particularly in certain subgroups of patients. Current clinical opinion holds that surgery be considered for patients with cerebellar hemorrhage, particularly if the diameter exceeds 3 cm, and for young patients with significant hemispheric hemorrhage experiencing clinical deterioration.[234]

In spite of the potential wide applicability of anti-hypertensive therapy following ICH very little data is available regarding this intervention. Both studies included had very small numbers and were significantly hampered by lack of measurement of clinical effect. The study examining intravenous ketanserin on arterial and intracranial pressures in a small group of patients raises the possibility that cerebral perfusion pressure might be affected by anti-hypertensive therapy.[90]

Role of Thrombolysis in Stroke

Stroke due to vascular occlusion (ischemic stroke) comprises 80% of all stroke.[235] The mechanisms of occlusion are varied but have in common the deposition of platelets and fibrin. Fibrin is a protein that is deposited in strands enmeshing red blood cells and platelets alike. Plasminogen is released from the vascular endothelium and converted to plasmin by plasminogen activator and plays a role in regulating the duration and propagation of clots within the body. The human gene can be spliced into bacteria to allow for large-scale production of tPA and harvested in commercially viable quantities. Genentech received FDA approval for its use in the coronary circulation in 1987 with subsequent use in acute occlusions of the coronary arteries.

Prior to the publication of the NINDS Trial of IV rtPA delivered within 3 hours of stroke onset,[236] no acute therapy had been shown to modify the outcome of ischemic stroke in human trials. Two potential interventions for acute ischemic stroke therapy were: 1) re-establishing blood flow prior to cell death, and 2) limiting irreversible damage in ischemic brain. Efforts had been mainly directed at reducing neuronal metabolism[49,237] neuroprotection,[238] and antioxidation.[239] While the sequence of molecular events which led from energy failure through membrane depolarization, cytotoxin release, calcium influx with subsequent activation of destructive enzymes had been well worked out;[239] attempts to influence the process in humans had been ineffective.[240,241] Preclinical work on rodent models of these interventions had been highly successful, suggesting a profound disconnection between animal models of stroke and the human syndrome studied in clinical trials. Several reasons have been suggested for this failure to translate laboratory results into clinical outcomes.

Animal models have focused on short time periods of drug administration and outcome evaluation with a focus on anatomic measurements (volume of infarct) rather than functional goals.[241] While consideration of such trials has not stopped,[241,242] the results suggest a need for a renewal of efforts on reversing vascular occlusion prior to the development of irreversible cellular damage.

Thrombolysis enjoys a prominence in acute stroke due to this critical role of reestablishing perfusion in the face of repeated failure of other strategies. It is the only medical treatment approved for acute ischemic stroke in the U.S. and Canada. The stroke community in North America has embraced this treatment for acute stroke.[66,243-245] However, the evidence supporting this treatment rests on substantially fewer trials and numbers of patients than that accumulated for cardiac ischemia.

Subsequent guidelines suggested that tPA should be used within 3 hours of stroke onset.[53] Similar recommendations followed in Canada from the Canadian Stroke Consortium[246] with the recommendation that use be limited to sites with personnel with experience in acute stroke care. Post-marketing surveillance mandated by HPB and maintained by the CASES database[247] demonstrated a treatment rate in Canada of 6% of all stroke.[59] Variability was noted in treatment rates between sites. There are currently nine designated stroke centers in the Province of Ontario with rates of thrombolysis ranging from 2.9% to 20.6% for the period July to December, 2002.[248]

Our search for references examining the effectiveness of thrombolytic therapy for acute stroke identified 343 reviews. Of these, the majority did not consider intravenous tPA, acute stroke or were narrative reviews. One[195] analyzed the relationship between onset to treatment time and outcome and is further discussed under Intervention F. This left two reviews for inclusion.[249,250]

Wardlaw and colleagues[249] reviewed 18 trials including 5727 patients. Sixteen were double blind and while a variety of thrombolytic agents were used, 50% of the patients in trials included utilized intravenous tPA. Overall, thrombolytic therapy administered in the 0 to 6 hour window decreased the proportion of patients who are dependent at three to six months (odds ratio 0.84, 95% CI, 0.75-0.95). Patients treated within this time frame also had greater odds of death at the end of 3 to 6 month follow-up (odds ratio 1.33, 95% CI, 1.15-1.53). For patients treated within the 0 to 3-hour window, death or dependency was reduced further (OR 0.66, 95% CI 0.53-0.83) with no increase in the risk of death (OR 1.13, 95% CI, 0.86-1.48). Some heterogeneity of effect was noted. Data on ethnicity was not available. The reviewers did comment that there was limited data on patients over the age of 80. Graham and colleagues[250] conducted a meta-analysis regarding the safety of tPA for acute ischemic stroke. Fifteen published open-label studies including 2,639 treated patients were included. In spite of an overall rate of protocol violation of 19.8%, the symptomatic intracranial hemorrhage rate was 5.2% (95% CI, 4.3-6.0). This compared favorably with the NINDS Trial rate of 6.4%. Of significance, however, was the cross study correlation of mortality rate with protocol violation rate ($r=0.67$, $p=0.018$).

North American Post-Marketing Experience

The largest published post-marketing cohort was the Standard Treatment with Alteplase to Reverse Stroke (STARS) study.[225] This group of 389 had baseline characteristics similar to

NINDS with comparable outcomes. The symptomatic intracranial hemorrhage rate was 3.3% with 35% of treated patients having minimal or no disability at one month.

A report from Cleveland was initially worrisome in showing high rates of complications. In particular, the symptomatic ICH rate was 20%—more than double that seen in the NINDS trial and far higher than the NINDS placebo hemorrhage rate of 0.6%.[72] The authors noted a protocol violation rate (most frequently time criteria) of greater than 50% and subsequently instituted a quality improvement program in participating institutions, following which the experience was reevaluated.[73] Significant improvement was noted with a symptomatic ICH rate of 6.4% in the face of a protocol deviation rate of 19.1%.

tPA received provisional approval in Canada on February 16, 1999.[247] As a condition of approval, a prospective cohort of patients treated with tPA was mandated (Canadian Activase for Stroke Effectiveness Study [CASES]).[59] The resulting dataset assembled from 25 academic and 35 community sites contained 1,135 patients and is the largest such group yet assembled. This prospective cohort was collected between February 17, 1999 and June 30, 2001. Outcome data was assessed at 90 days with central reading of the initial and 24-hour scan to ensure an unbiased estimate of the hemorrhage rate. Eighty-four percent of all cases treated in the country were included, based on a comprehensive survey of all Canadian hospitals with CT scanners and an on site audit of four randomly selected centers. Neither the rate of excellent functional recovery defined by mRS 0, 1, 2, (38.6%) or the rate of intracranial hemorrhage (4.5%) differed significantly from that observed in the NINDS trial .[59] A protocol violation rate of 13.8% was noted with the majority being time violations (treatment over 3 hours). The distribution of outcomes for those with protocol violations did not differ significantly from the group as a whole. Such outcomes have been reflected in several other observational studies.[59]

Intervention A: Does Surgery Impact the Outcome in Patients with Acute Intracerebral Hematoma (ICH)?

ICH represents approximately 9% of the 700,000 strokes which occur in the U.S. every year.[7] Significant morbidity and mortality is associated with this condition.

Older studies on surgical treatment of ICH are hampered by the low sample sizes. Only the study by Morgenstern[87] and Batjer[120] provided power calculations. Sample size was limited by poor accrual in the SICHPA trial[88] and by a perception of futility in the Batjer trial.[120] In addition to poor power, the low sample size increases the possibility of baseline imbalances. With the notable exception of Batjer,[120] the management, particularly in the control or medical arm, was poorly specified. Potentially important covariates such as intracranial pressure, hypertension, glucose control, and the institution of mechanical ventilation, were either not specified or unreported. None of the included studies specified blinded outcome assessment. In addition, all studies included patients with supratentorial hemorrhage and no studies included patients with infratentorial hemorrhage.

The STICH trial,[122] which accrued 1,033 patients, overcame a number of the issues which limited the early trials. The time window for surgical treatment was rather large at 24 hours. Further, the method of clot evacuation was not pre-specified. The mean time between ictus and randomization was long, at 22 hours. Thus, the possibility that early treatment with minimally-

invasive surgical modalities improves outcomes. Finally the primary endpoint was measured in a blinded fashion.

Our meta-analysis does not preclude a benefit for treatment. The point estimate favors surgery, with the confidence interval crossing the null (Figure 2). Given the issues identified above, a well-designed, appropriately powered prospective evaluation is required.

Intervention B: Does Antihypertensive Treatment Reduce Stroke-Related Mortality and Disability in Patients with Acute ICH?

Brain injury in ICH is due to direct mechanical injury related to expanding clot, increased intracerebral pressure (ICP), herniation secondary to mass effect and the toxic effects of extravascular blood. Patients who have an ICH often have an acute rise in systemic arterial pressure (BP) and this may be beneficial to maintain cerebral perfusion pressure (CPP). CPP is the difference between mean arterial pressure and ICP. This elevation in BP may also put the patient at increased risk of extension of the hemorrhage.

Nishiyama et al.[91] was a small study, which did demonstrate a decrease in CPP. In this study this reduction did not lead to any adverse clinical outcomes suggesting some concern regarding safety; albeit with a very limited population. Current American Heart Association writing group guidelines suggest that the management of elevated blood pressure in patients with ICH be individualized based on the patient's age, history of hypertension, presumed cause of hemorrhage and interval since onset.[251] For patients with a history of hypertension it is recommended that the mean arterial pressure be maintained at less than 130 mmHg by this writing group.

In spite of wide applicability and potential simplicity of antihypertensive treatment after intracerebral hemorrhage, the data available to informed clinical decision making is extremely poor. Choice of agent, modality of treatment and timing all remain open questions. A new large trial which addresses some aspects of the clinical questions is required.

Intervention C: Does IA Thrombolysis Reduce Stroke-related Mortality and Disability in Adults with Acute Ischemic Stroke?

The study by Keris[93] used sequential randomization, suggesting that allocation concealment was incomplete. Further assessment was not blinded and the analysis was not performed on an intention-to-treat basis. These methodology issues raise questions about the conclusions of this trial. PROACT I and II demonstrate the possibility of using IA therapy to establish reperfusion. Further, PROACT II suggests that recanalization of vessels achieved within the six-hour window can result in a significant clinical improvement. Enlarging the time window for acute thrombolysis would potentially increase the number of patients treated. Of concern are the very large number of patients who need to be screened and subjected to angiography to achieve this

result. Interventional therapy is thus a very resource-intensive course to follow in acute stroke. More accessible forms of acute imaging to establish vessel occlusion such as CT or MR angiography may be helpful in improving on the odds of receiving treatment after screening. Such noninvasive methods might decrease procedure related complications and enhance safety by eliminating individuals without vessel occlusion from potentially hazardous treatment albeit at a cost of adding time to treatment.

The EMS Bridging Trial[94] is a Phase I trial demonstrating the feasibility of combined treatment, combining IV and IA treatment as the possible advantage of reducing the time to canalization. This study demonstrates feasibility and results of a larger trial currently underway is awaited.

A new trial of intra-arterial treatment would be helpful in patient selection. In particular the timing since symptom onset, thrombus location and criteria for combining with IV therapy remain to be elucidated.

Intervention D: Does Treatment to Normalize Blood Glucose Levels Reduce Stroke-Related Mortality and Disability in Adults with Acute Stroke?

Weir and colleagues analyzed the outcomes of 750 non-diabetic patients in an attempt to correlate plasma glucose with clinical outcomes.[252] Of some 750 patients included in the model, 86% had ischemic stroke while the remainder were cerebral hemorrhages. Hyperglycemia with serum glucose greater than 8 mmol/L predicted a poor chance of survival and independence. This effect was persistent after adjusting for age, stroke type and severity. This observation suggests that elevated serum glucose is more than a marker for severe vascular event. As hypoglycemia can be a significant detrimental influence on neurologic outcome, randomized trial evidence should be obtained prior to advocating specific treatment protocols particularly in the setting of modest elevations of plasma glucose.

Neither of the included studies[95,96] addressed our question on whether treatment to normalize blood glucose levels would reduce stroke related mortality and disability in adults with acute stroke. The study of Gray et al.[95] did demonstrate that without specific intervention, plasma glucose values do decrease 24 hours after stroke but we still do not know whether treatment will lead to improved outcomes.

Current consensus guidelines in the absence of evidence recommend lowering glucose levels above 16.63 mmol/L.[253] Glucose values decreased 24 hours after stroke; however, it is unknown whether treatment will lead to improved outcomes. Further trials examining this issue are required.

Intervention E: Does Mechanical Thrombus Disruption Reduce Stroke-Related Mortality and Disability in Adults with Acute Ischemic Stroke?

Both included studies compared continuous ultrasound monitoring during acute thrombolysis with no such monitoring.[97,111] The observation of early recanalization is consistent across both of these studies. Eggers et al. reports a benefit in the small group studied (n=25) for treatment only in the Barthel Index, with no significant benefit in mortality or mRS score.[97] Alexandrov[111] demonstrated superior efficacy for early recanalization and the prespecified endpoint of early dramatic recovery (decrease in the NIH Stroke Scale Score of 10 points on a NIH Stroke Scale Score of less than or equal to 3), but no significant differences between the two groups at 3 months. While these results are encouraging, a larger trial to ensure both the safety and efficacy of this treatment modality is required. Particularly critical is establishing an enduring benefit by reducing mortality, disability or both at 3 months. Alexandrov[111] points out that the results may not be generalizable as use of the modality requires skill and experience. Other mechanical modalities including balloons, suction devices, and mechanical clot extraction modalities have yet to report randomized results.

A phase I study of the MERCI mechanical embolus retrieval device was published recently.[254] Twenty eight patients were studied with a mean time from onset to treatment of just over 6 hours. Successful recanalization was achieved in 43% patients using embolectomy alone. This increase of 64% when intra-arterial tPA was added. This early publication is of interest and further study of these devices is warranted. In the small number of papers published, patient selection and interaction with other modalities such as intra-arterial tPA remains unclear.

Future well-designed studies investigating mechanical thrombus disruption to reduce stroke-related mortality and disability are needed.

Intervention F: Is the Effectiveness and Safety of Thrombolytic Therapy for Adults with Acute Ischemic Stroke Affected by Time from Onset to Treatment?

Hacke and colleagues, writing for the ATLANTIS, ECASS, and NINDS tPA study group investigators, provided a patient-level meta-analysis of the relation between onset to treatment time and outcome for thrombolysis.[195] Data from six trials that had treatment windows between 0 and 6 hours were obtained—NINDS Parts 1 and 2, ECASS 1 and 2, and ATLANTIS Parts A and B.[195] These included trials encompass 99% of patient data available from RCTs of tPA. The trials varied in the time inclusion criteria. Both NINDS trials were restricted to patients treated between 0 and 3 hours. The ECASS trials included patients treated between 0 and 6 hours. ATLANTIS A enrolled from 0 to 360 minutes while ATLANTIS B initially recruited from 0 to 300 minutes, and subsequent to the publication and acceptance of the NINDS data was narrowed to 180 from 300 minutes. Inclusion and exclusion criteria in the trials were similar. A diagnosis of acute ischemic stroke with CT evidence refuting hemorrhage was required. Patients at high risk of bleeding with thrombolytic therapy, including those who had had trauma or recent surgery, were excluded. Both the ECASS trials and ATLANTIS B excluded patients with early infarct signs on the baseline CT scan. This was not a requirement in the NINDS trials. Favorable outcome for the purposes of this analysis was defined as scores on the Rankin Scale of 0 or 1, Barthel Index of 95 to 100, and a NIHSS score of 0 or 1. These ranges represent minimal or no disability. A logistic regression model was constructed to assess the relationship between

onset to treatment time and favorable outcome at 90 days. A multivariable logistic regression model was constructed including possible confounding variables.

The final results were presented as an intention-to-treat analysis including patients on whom data was incomplete (n=2,775). The median age of this group was 68 years; 84.6% were White (non-Hispanic), 9.1% Black, 2% Hispanic, 0.9% Asian, with the remainder being from other ethnic backgrounds or unreported. The median baseline NIH Stroke Scale Score was 11 with a median onset to treatment time of 243 minutes. Of note, 67% of patients were treated beyond the 3-hour window. The final model included treatment, onset to treatment time, age, blood glucose, admission NIHSS, baseline diastolic pressure, interaction between age and NIHSS, and interaction between onset-to-treatment time, and treatment. An association was found between onset-to-treatment time and outcome. The odds ratio for favorable outcome with tPA treatment in the 0 to 90 minute interval was 2.81 (95% CI 1.75-4.50). This decreased to 1.15 (0.90-1.47) in the 271 to 360 minute interval. The 95% confidence interval of the adjusted odds ratio for favorable treatment remained above 1, indicating benefit for treatment until 270 minutes (4.5 hours) after onset of symptoms. Likewise, the adjusted odds ratio for death exceeded 1 only in the interval between 271 and 360 minutes. Interestingly, there was not a strong association between 3-month favorable outcome and baseline NIHSS in any time stratum. This also confirms a strong association between stroke outcome and time to treatment. Of significance, the relationship holds throughout the currently used therapeutic window of 0 to 3 hours.

Parenchial hematoma were seen in 5.3% of patients compared to 1.1% of placebo patients in multivariate modeling for hemorrhage, which included onset to treatment time (OTT), age, and NIHSS scores. The OTT and treatment interaction was not significant. Use of tPA and age increased the probability of hemorrhage but OTT and baseline NIHSS scores did not.

The prospective studies identified in this review did not prospectively validate treatment beyond the 3-hour window.[102,116] The study characteristics did not allow for a useful combination of results. Thus, this patient-level meta-analysis provides the best current summary of the evidence for a relationship between time to intervention and clinical outcomes.

Thus, it is imperative that systems be designed to provide treatment as soon as possible after onset of symptoms rather than aiming for treatment within 3-hours of onset. In addition, there is suggestion of benefit beyond the 3-hour window. This benefit is smaller than that in earlier time frames consistent with the overall results of the analysis. It is entirely possible that significant benefit accrues to a subgroup of patients treated beyond 3 hours. The suggestion of benefit in later time windows will require validation from prospective studies that may also provide the defining characteristics of the group most likely to benefit or conversely be harmed. Since a treatment effect in these later time windows is smaller than that observed earlier, larger groups of patients will need to be randomized.[195]

In Canada, tPA for stroke was commissioned in 1999 . The approving body required a prospective registry for safety in the context of routine care. Over 2.5 years, 1,135 patients were enrolled in 61 centers in Canada. For all patients 90 day outcome and hemorrhage rates were determine, along with baseline and 24 hour CT scans which were viewed centrally.

The median NIHSS scores were identical to that seen in the NINDS trial. Thirty six percent of the patients made a complete functional recovery and returned to the baseline state at 90 days. This result was not significantly different than the NINDS trial (p=0.15). The rate of symptomatic intracranial hemorraghe was 4.6% compared to the NINDS rate of 6.4%.[255]

Intervention G: Do Pretreatment CT Scoring Systems Affect the Safety and Efficacy of Thrombolytic Therapy for Acute Ischemic Stroke?

Prospective evaluation of CT scoring systems was not available, and both included studies are evaluations of CT's conducted during the course of prospective trials of thrombolysis in stroke. Barber and colleagues[256] evaluated 203 consecutive patients treated with thrombolytic therapy within 3-hours of prospective scoring of their CT scans according to a 10-point scale based on an unenhanced axial CT scan. The value was calculated from two cuts within the MCA territory. A normal scan obtained a score of 10 points with one point subtracted for each area of early ischemic change. The ASPECTS Score correlated with baseline NIH Stroke Scale Score in an inverse manner (Spearman's rho = -0.56, $p < 0.001$). An ASPECTS Score of less than 7 had strong predictive value for death or dependence. With dependence defined as a Rankin Score of 3 to 5, the odds ratio for good functional outcome was 82 (95% CI 23-290). Similarly, an ASPECTS Score of less than or equal to 7 was predictive of the presence of symptomatic hemorrhage (odds ratio 14, 95% CI 1.8-117). Good correlation was noted between the ASPECTS Scores of pairs of stroke neurologist/radiology trainees and the neuroradiologists (kappa = 0.85, 0.71, 0.89 respectively).

Retrospective application of the ASPECTS score to CT scans used in the PROACT II Trial suggests that those with an ASPECTS Score greater than seven were three times (OR 3.2, 95% CI 1.2-9.1) more likely to have an independent functional outcome when compared with controls, whereas, those with a score less than or equal to seven were much less likely to do so.

The wide availability of CT scanners along with the ease of use of the ASPECTS Score suggests this may become an important tool in treatment decisions.

Intervention H: Do Pretreatment MRI Scoring Systems Affect the Safety and Efficacy of Thrombolytic Therapy for Acute Ischemic Stroke?

The time frames used in patient selection for thrombolysis represent surrogate measures of viable tissue. Perfusion and diffusion weighted MRI scanning raise the possibility of patient selection on the basis of the demonstration of viable tissue with impaired perfusion. Perfusion weighted imaging (PWI) allows visualization of altered areas of blood flow.[257] Energy failure with the resulting inability to maintain water and ionic gradients results in decreased diffusion of water in the brain.[258]

Butcher and colleagues[259] have suggested that quantitative PWI mapping may be useful in predicting the fate of tissue. Thirty-five patients with acute stroke, 17 of whom were treated with tPA, were imaged within 6 hours of onset. The mean transit time was found to be prolonged in infarcted areas relative to salvaged areas ($p=0.001$) with an approximately 10% reduction in regional cerebral blood flow ($p=0.01$). From this study, the mean transit time appeared to be the

perfusion measure most predictive of outcome though delineation of absolute perfusion thresholds resulting in infarction could not be accomplished. This may, in part, be due to the dependence not only on absolute perfusion but also the duration of hypoperfusion. The interaction between these two measures is difficult to arrive at through the use of a single image during the course of an infarction.

Nevertheless, MRI definition of salvageable tissue versus tissue irreversibly committed to infarction when applied prospectively has the potential to enhance both the safety and efficacy of thrombolysis.

Intervention I: Do CT Perfusion/Angiography Affect the Safety and Efficacy of Thrombolytic Therapy for Acute Ischemic Stroke?

Prospective use of CT perfusion and angiography techniques in patient selection for thrombolysis was not identified. The two studies included demonstrate correlation of outcome with findings on CT angiography or CT perfusion techniques including Xenon CT. CT angiography permits the identification of large vessel occlusion without the risk of invasive techniques and thus has potential applicability in identifying patients who may benefit from invasive forms of revascularization (IA thrombolysis or thrombus retrieval). As noted above for Intervention H, the availability of physiologically-based criteria to select individuals with salvageable tissue presents the opportunity for significant benefit. In this regard, a CT is cheaper and more widely available than MRI scanning. Further MRI scanning has the potential to add increased time prior to treatment and decrease numbers available for treatment due to MR exclusion criteria, which include ferromagnetic foreign substances, claustrophobia and the requirement to closely monitor unstable patients.

The impact of the study by Kilpatrick[102] is limited by the small number of patients and biases inherent in selecting this particular group of patients for study. Nevertheless, the hypothesis that low cerebral blood flow as demonstrated on Xenon CT or major vascular occlusion is associated with infarct, and presumably worse clinical outcome, deserves more detailed prospective study as this may aid in singling out patients who may benefit from more aggressive therapy and furthermore those in which the risks of more aggressive therapy are warranted.

Intervention J: Are Community Education Programs Effective in Reducing Stroke-Related Disability and Mortality?

Both included studies demonstrate that multi-faceted educational and system changes for the provision of acute stroke care increased utilization of tPA. Given the complexity of this intervention we are unable to determine what components of this intervention led to the increased utilization. It remains unclear if community education programs are effective in

improving outcome in acute stroke. A number of similarities exist with the care of acute cardiac ischemia and it is instructive to examine the parallel and data in this field for relevance to stroke.

Ischemic heart disease is the leading cause of death in Canada and other industrialized countries.[260] Myocardial death under ischemic conditions is a time dependent phenomenon requiring a series of biochemical events and is not simultaneous with the onset of ischemia.[261] As is the case in stroke, this time dependence provides an opportunity for therapeutic intervention and early treatment of myocardial infarction has been shown to decrease infarct size and reduce mortality.[262,263] Rapid access to emergency treatment requires prompt identification of symptoms by patients or bystanders and presentation to an appropriate facility. Reperfusion of ischemic tissue can then be achieved through thrombolysis or angioplasty with the effectiveness of therapy being contingent on speed of delivery.[262-264] Patient delay in seeking care in North America is several hours and is felt to contribute to lower than expected outcomes from the application of available procedures.[264] Prompt and appropriate application of such resource intensive procedures might be expected to improve outcomes. Increased awareness of symptoms and need for urgency amongst patients might result in reduced delay and increase rates of thrombolytic treatment.

As acute myocardial infarction is the presenting symptom of ischemic heart disease in a substantial percentage of patients, a campaign aimed at unselected members of the community would be expected to reach the greatest members of people expected to benefit. Previous experience with community interventions in this area spans two decades, far longer than the experience in acute stroke. The REACT trial, reported by Luepker, was a RCT of the efficacy of community intervention on delay time employing cluster randomization of twenty U.S. cities into matched control and intervention pairs.[69] The design of the intervention was complex and involved expects in health behavior and epidemiology. The process of intervention design and its theoretical framework is extensively described in a companion publication.[265] ED staff in study hospitals were trained in standardized questioning of patients regarding the nature and onset of acute symptoms. Matched pairs of cities were comparable in age distribution, education level, ethnic distribution, median income and baseline median delay time from symptom onset to presentation. Delay times were log transformed to obtain a more normal distribution. The trend of delay time was calculated by linear regression of log delay against calendar time adjusted for the patient level covariates: age, sex and past history of coronary artery disease. The trends were then compared pair wise with the matched communities. Delay times were available for 73% of the population of interest. A baseline period of four months was compared to the intervention period of eighteen months. The study had an 80% power to detect an end of trial difference of 30 minutes between intervention and control groups. During the study period mean delay time dropped by about 10 minutes in both the reference and intervention groups. The primary outcome response, which was the slope difference (%/yr) between intervention and reference groups, was 2.3% (95% CI -5.5 to 10.8). The intervention was consequently felt to be ineffective.

This result in a methodologically superior design to those carried out in the field of acute stroke is of concern. Application of ineffective strategies, at a minimum, diverts resources away other applications. Further, there is the possibility that a campaign which increases the number of patients presenting with potential stroke increases the probability of false positive diagnoses and, thereby, worsen outcomes.

Intervention K: Are Designated Centers Effective in Reducing Stroke-Related Disability and Mortality?

Studies evaluating the brain attack coalition definition of a stroke center were not identified. Thus, each study reviewed in this section had a different approach in development of a stroke center. Each study did demonstrate decreased time intervals in the treatment continuum from presentation through the hospital stay. The percentage of patients treated is a significant surrogate measure of outcomes and, assuming the treatment meets the NINDS protocol, one might infer that improving the percent of patients treated would result in improved outcomes. None of these studies demonstrated adequately that their strategy led to decreased stroke morbidity and mortality. At present, the potential effect of the establishment of a stroke center according to the pre-specified definition is not known and waits empiric validation. The magnitude of the effect may depend on the pre-existing infrastructure, geography and demographics of the area served. While the need for such a validation may not be readily apparent it impacts significantly on resource allocation in a competitive economic environment and has broader implications for public health.

One possible alternative with Stroke Centres strategy is dispersing the expertise through the use of Telemedicine. Technology currently exists which permits the visualization and examination of both the patient and the scan at a location remote from the examining physician. While this would transfer physician expertise in the treating center (i.e. nursing, radiology, technology, and/or laboratory support). Comparisons of each approach would be helpful in further stroke system planning.

Intervention L: Are ED Protocols for the Management of Acute Stroke Effective in Reducing Disability and Mortality?

At this time, we were unable to identify any studies that addressed our research question of whether ED protocols for the management of acute stroke are effective in reducing disability and mortality. The studies by Smith et al.[106] and Jahnke et al.[118] evaluated ED protocols and document the time to treatment with thrombolytics. Smith et al.[106] compared the times to treatment in patients in their study with historical data and conclude that their ED protocol yields similar times to treatment than previously published in the original trials[231] Jahnke et al.[118] compared the time to thrombolytic treatment between those who received treatment in the first year of the protocol and the second year. They document an improvement in time to treatment in the second year of the protocol though outcomes are not reported. The last study by Akins et al.[117] compared patients who had their treatment initiated by the ED physician versus the neurologist. The patients had similar presentations and baseline risks and there were no differences in outcomes between these two small groups. Initially they identified more protocol violations by the ED physicians as well as a shorter time interval to treatment by the neurologist. This study did not demonstrate any difference in outcome between the ED physician treatment and neurologist treatment but the study size was very small and with the increased protocol violations and increased length to treatment there is the possibility that in a larger study worse outcomes would be found with this model.

The studies available were limited in methodology and outcomes assessed. In particular, the clinically significant outcomes of mortality and morbidity were not examined.

Limitations

Our literature searches were restricted to English language publications. Although, this limited our review it is unlikely that it biased the results in any meaningful way.[74,75]

Our levels of evidence "guiding principle" was to limit our review to include reports of RCTs, whenever possible. There is debate within the literature as to the merits of excluding reports of high quality observational studies from addressing questions within a systematic review.[266-269] There is little empirical data as to whether the inclusion of such studies introduced bias into the results. We elected to take the more conservative scientific position of providing 'bias free' estimates of effectiveness whenever possible. Quality assessing observational studies, and designs is problematic. There is no published validated scheme available. We used the NOS for assessing quality, and while we believe it has some appropriate psychometric properties, the index itself is unpublished. There is some data which suggests that assessments using unpublished systems as a grading system might introduce bias.[270]

In spite of the clear indication that early time to treatment improves outcomes and the complexity of the multilevel interventions required to accomplish these targets, a limited number of studies were available for review in all areas examined in our report. This may reflect a bias, which does not equate system interventions with medical therapies. With the significant exception of thrombolytic therapy for acute ischemic stroke, methodologic inadequacies were apparent in all topic areas. Further detailed information on the influence of patient characteristics (e.g., race) on outcome was either unavailable or unreported.

We identified a meta-analysis examining surgical intervention for ICH that was published in 2002,[233] which presented data from two trials that were not identified by our search strategy. Our search did not capture these references, since the study by McKissock et al. was published in 1961, prior to our search date of 1964. The study by Chen (1992) is a non-English language citation and hence, was not captured since our search was limited to English language citations. Chen et al. was a large RCT investigating surgical intervention for ICH. We were able to extract enough data from the meta-analysis pertaining to mortality outcomes to include this data in our meta-analysis as a sensitivity check (Figure 4). We were less inclined to extract data from the McKissock et al. results since it was determined that the surgical methodology for ICH had substantially advanced since the time that this report was published and hence, would have been heterogeneous with other studies included in our review.

Five studies examined IA thrombolytic therapy for ischemic stroke. Due to heterogeneity of interventions and comparisons, we obtained pooled estimates based on only two studies.[92,110] We excluded Keris et al.[93] because they did not provide 90-day follow-up assessment data and there were concerns regarding methodology of the trial. Lewandowski et al.[94] randomized patients to IV tPA and IA tPA or to IV placebo and IA tPA. So the contrast between the two groups is IV tPA versus IV placebo. Conceptually, this study was not combinable with the other studies.

The effect measure selected for pooling the outcomes of death and death and disability was the odds ratio. Other effect measures suitable for dichotomous outcomes including the relative risk and absolute risk reduction could also be considered, and might show different results. However, the odds ratio has several statistical advantages, one being it has been shown to frequently exhibit less heterogeneity than other effect measures.[271] In addition, the odds ratio was used in a previous meta-analysis, which could facilitate comparison.

For surgical interventions for ICH, there was evidence of some statistical heterogeneity, although not statistically significant. It should be noted, however, that tests of heterogeneity in meta-analysis are recognized to have limited power, particularly when the number of studies is small.[272] We used random effects methods to adjust for statistical heterogeneity, which results in wider confidence intervals for the pooled estimate. Furthermore, random effects pooled estimates should be interpreted with some caution.

Research and Clinical Implications

ICH

In spite of the significant morbidity and mortality associated with ICH, and the potential negative effects of pressure and blood products within the brain, surgical evacuation of the hematoma remains unproven. Randomized trials did not include cerebellar hematomas, and thus, these findings cannot be implied to hematomas in the posterior fossa. In spite of the negative data, our results do not preclude the possibility of a benefit from surgery. There was some heterogeneity within trials and the pooled point estimate favored surgery, albeit with a large confidence interval. Further trials in this may be helpful. Such trials should likely be conducted in a multi-center format, since single-center trials suffer from low patient accrual. Both the non-surgical interventions and outcome collection will need to be standardized. In particular, principles of withdrawal of care should be established for such trials as part of the protocol, and monitored subsequently. The perception of futility amongst caregivers and families may influence behavior and invalidate trial results. Areas specifically requiring further delineation include timing and type of surgery. Minimally invasive surgery has increased in utility in many areas and thus data from older trials may not be sufficient to exclude new technologies.

Antihypertensive therapy has not been well studied in patients with ICH. Hypertension remains a significant risk factor for hemorrhage, and thus, may well impact on clinical outcomes including the rate of hematoma expansion and recurrent hemorrhage in the setting of acute ICH. Antihypertensive therapy has potential wide application in this group of patients. Until such time as further data is available, guidelines provide a reasonable basis for the clinical management of ischemic stroke.[251]

Timing, modalities of treatment, and treatment target remain open issues for further research.

Acute Ischemic Stroke

IV thrombolysis with tPA remains the sole approved intervention for acute ischemic stroke. Data from primary trials and meta-analyses suggests a significant benefit of treatment in the window from 0 to 3 hours after stroke onset. Individual patient-level meta-analysis suggests that earlier treatment significantly improves outcomes and systems should be designed so as to provide treatment to eligible patients as soon as possible after stroke onset.

A paucity of data is available regarding the outcomes of specific subgroups of patients. In particular, further data should be sought regarding outcomes in specific ethnic groups, the elderly (over the age of 80), and specific stroke subtypes. At present, there is no data to suggest any group identified on the basis of these characteristics should be excluded from treatment.

Regression analysis of the relationship between onset to treatment time and outcome, suggests that there may be benefit for thrombolytic therapy up to 4½ hours after onset. It is clear, however, that the odds ratio for good improvement drops significantly for the 3 to 4½ hour time frame compared with earlier time frames. Prospective trial data for benefit beyond 3 hours is lacking, and the selection of patients most likely to benefit from therapy within this time window remains a challenge. It is likely that development of imaging techniques in this group will identify the minority of patients capable of benefiting in this time frame. Further data should be specifically sought with regard to the subgroup of patients who may benefit beyond the three-hour window. Likewise, information on the relative risk of hemorrhage in the current treatment window would be helpful.

IA therapy has prospective evidence to suggest a benefit up to 6 hours after onset. However, the pooled effect estimates, suggest that the benefit is not robust. Centers capable of delivering this treatment, however, may use it in those patients outside the traditional IV-treatment window who are not candidates for IV tPA. There may be further benefit in combining this treatment with IV therapy; this is the subject of upcoming combination trials. Intra-arterial therapy requires a significant investment of resources. In addition, as compared to intravenous therapy, the time to treatment is likely to be increased due to the invasive and specialized nature of the therapy.

Time since onset of symptoms remains a surrogate for the pathophysiologic state of affected tissue. Ideally, the goal of pre-treatment diagnostic analysis should be the identification of viable tissue in which infarction can be prevented by reestablishing blood flow. Both CT and MRI techniques hold promise in this regard. MRI, through multi-modality and multi-planar techniques, may be the examination of choice in the future. Limitations due to expense, additional time, and MR exclusions remain to be overcome, however. Simple CT scoring systems, such as ASPECTS and CT perfusion/angiography, provide similar data in a shorter time frame. As CT scanners are more widely distributed, these techniques remain a viable option. The literature to date, however, has not employed these techniques prospectively to make treatment decisions. Thus, the information from imaging techniques must be taken in the clinical context including onset to treatment time and current approved treatment protocols and balancing probable efficacy with risk. Further work is expected to define subgroups in whom these techniques are likely to be of most benefit; for instance, those in whom the onset time is not known or those who fall outside traditional treatment windows. In addition, reliable

identification of patients without probability of benefit will enhance treatment efficacy by eliminating them from further therapy.

Acute stroke therapy exists within a system framework capable of timely identification of acute stroke, triage, and delivery of effective therapy. These systems include a pre-hospital and in-hospital phase. Given the strong link between outcome and onset to treatment time, an effective means to alter behavior of the public to permit rapid identification of acute stroke and the engagement of EMS, is helpful. The data in this regard, however, suggests that the traditional approaches using advertising strategies, have limited evidence for a benefit in stroke and evidence for a lack of benefit in cardiac ischemia. Further work regarding effective means of altering behavior in the context of acute stroke is required. As noted above, compelling evidence exists to suggest that outcomes are strongly related to the time required to deliver therapy. Systems of care including EMS, designation of treatment sites, and in-hospital protocols remain the only means to achieve this outcome. In spite of the critical importance of these systems, little empiric evidence exists as to their efficacy and, further, the relative efficacy of various components of the system. Until such time as this evidence is forthcoming, each aspect of the system will require efforts at validation.

Conclusions

Currently, available data do not support a role for surgery in the treatment of acute intracerebral hemorrhage. Results, however, do not preclude benefit from surgery which involves modalities other than those studied in the acute trials (e.g. Minimally invasive technologies) or treatment of hemispheric hematoma at very early timeframes. In spite of potential importance, available therapies and ease of administration of antihypertensive agents, very little data exists to suggest that their use is of benefit in the setting of acute ICH. Further studies are required in this area.

IV thrombolysis with tPA is effective and efficacious for acute ischemic stroke. The effectiveness is strongly linked to time since onset of symptoms with shorter times demonstrating significantly better outcomes. Intraarterial therapy remains an option for a subgroup of patients with large vessel occlusions principally in the middle cerebral artery distribution who are not candidates for IV tPA. The evidence for this intervention, however, remains less robust than for IV therapy. Limited data is available regarding patient characteristics predicting outcome. The system changes required to ensure prompt delivery of appropriate therapy are complex and operate on multiple levels. In spite of their critical role, little data exists regarding the efficacy of these interventions and, in particular, the relative efficacy of various components with regard to patient outcomes.

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Appendix A. Search Strategies

Search Strategy 1

Ovid Medline
1. Intracranial Thrombosis/ or Cerebral Infarction/ or Cerebral Hemorrhage/ or Cerebrovascular Accident/
2. "Intracranial Embolism and Thrombosis"/
3. Intracranial Embolism/
4. Brain Ischemia/
5. ischemic stroke$.tw.
6. cva.mp.
7. or/1-6
8. Intracranial Thrombosis/ or Cerebral Infarction/ or Cerebral Hemorrhage/ or Cerebrovascular Accident/ or "Intracranial Embolism and Thrombosis"/ or Intracranial Embolism/ or Stroke/ or Brain Ischemia/
9. (stroke or cva).mp.
10. or/8-9
11. Intracranial Thrombosis/ or Cerebral Infarction/ or Cerebral Hemorrhage/ or Cerebrovascular Accident/ or "Intracranial Embolism and Thrombosis"/ or Intracranial Embolism/
12. stroke/
13. exp Intracranial Hemorrhages/
14. (cerebrovascular$ or cerebral vascular or stroke).tw.
15. (haemorrhag$ or hemorrhag$ or haematom$ or hematom$).mp.
16. (ich or cva).mp.
17. (primary intracerebral hemorrhage or pich).mp.
18. (haemorrhag$ or hemorrhag$ or haematom$ or hematom$).mp.
19. exp brain/
20. (cerebr$ or intracerebral or intracran$ or parenchymal or brain).tw.
21. 18 and (19 or 20)
22. or/11-17,21
23. *subarachnoid hemorrhage/ or *subarachnoid hemorrhage, traumatic/
24. *Tissue Plasminogen Activator/
25. 22 not (23 or 24)
26. exp surgery/
27. surgery.hw. or surgery.kw.
28. surg$.mp.
29. endoscop$.mp.
30. craniotom$.mp.
31. stereotactic.mp.
32. ventricular drain$.mp.
33. intraoperative ultras$.mp.
34. neuroprotective.mp.
35. or/26-34
36. 25 and 35
37. *Cardiac Surgical Procedures/
38. *Coronary Artery Bypass/
39. *Coronary Disease/
40. *Aortic Valve Stenosis/
41. *Endarterectomy, Carotid/
42. or/37-41
43. 42 not (11 or 12 or 13)
44. 36 not 43
45. Antihypertensive Agents/ or Hypertension/ or Angiotensin-Converting Enzyme Inhibitors/

46. antihypertensive treatment.mp.
47. antihypertensive$.tw.
48. (angiotensin-converting enzyme or ace).tw.
49. Labetalol/
50. 36894-69-6.rn.
51. (Chlortalidone or Hydrochlorotiazide).tw.
52. (Atenolol or Propranolol or metoprolol or carvedilol or labetalol or pindolol or bisoprolol).tw.
53. (Enalapril or lisinopril or captopril or ramipril or benazepril).tw.
54. (losartan or candesartan or valsartan).tw.
55. (nifedipine or nicardipine or amlodipine or isradipine or varapamil or felodipine or diltiazem).tw.
56. (nitroprusside or clonidine or terazosin$ or doxazosin$).tw.
57. or/45-56
58. *subarachnoid hemorrhage/ or *subarachnoid hemorrhage, traumatic/
59. *Tissue Plasminogen Activator/
60. 57 not (58 or 59)
61. 60 and 25
62. injections, intra-arterial/
63. intraarterial.tw.
64. intra arterial.tw.
65. or/62-64
66. thromboly$.tw.
67. thrombolytic therapy/
68. (iat or ia).tw.
69. exp Tissue Plasminogen Activator/
70. tPA.mp.
71. Activase.tw.
72. alteplase.tw.
73. clot dissolv$.tw.
74. reperfusion therapy.tw.
75. reteplase.tw.
76. tenecteplase.tw.
77. tissue plasminogen activator.tw.
78. tPA.tw.
79. EC-3-4-21-68.rn.
80. or/66-79
81. 65 and 80
82. blood glucose.mp.
83. Blood Glucose/
84. serum glucose.mp.
85. blood sugar.tw.
86. ((blood or serum) adj2 (sugar or glucose)).mp.
87. Hyperglycemia/
88. Hypoglycemia/
89. or/82-88
90. ((mechanical or ultrason$) adj (clot$ or disrupt$)).mp.
91. ultrasonic therapy/
92. Angioplasty/ or Angioplasty, Balloon/
93. endovascular intervention$.tw.
94. snare manipulation.tw.
95. guidewire.tw.
96. mechanical thromboly$.tw.
97. mechanical recanalization.mp.
98. (percutaneous transluminal angioplast$ or pta).tw.
99. cerebral angiograph$/
100. or/90-99

101. exp Tissue Plasminogen Activator/
102. tPA.mp.
103. Activase.tw.
104. alteplase.tw.
105. clot dissolv$.tw.
106. reperfusion therapy.tw.
107. reteplase.tw.
108. tenecteplase.tw.
109. tissue plasminogen activator.tw.
110. tPA.tw.
111. EC-3-4-21-68.rn.
112. or/101-111
113. exp Tissue Plasminogen Activator/
114. tPA.mp.
115. Activase.tw.
116. alteplase.tw.
117. clot dissolv$.tw.
118. reperfusion therapy.tw.
119. reteplase.tw.
120. tenecteplase.tw.
121. tissue plasminogen activator.tw.
122. tPA.tw.
123. EC-3-4-21-68.rn.
124. or/113-123
125. mri.mp.
126. mr imag$.mp.
127. magnetic resonance imag$.mp.
128. magnetic resonance imaging/
129. 124 and (or/125-128)
130. health promotion/
131. health education/
132. Health Knowledge, Attitudes, Practice/
133. health behavior/
134. Attitude to Health/
135. delivery of health care/
136. program evaluation/
137. Marketing of Health Services/
138. Information Services/
139. advertising/
140. patient education/
141. community health planning/
142. area health education centers/
143. outreach.tw.
144. communications media/
145. health promotion.tw.
146. (community adj8 intervention).tw.
147. (advocacy adj5 program).tw.
148. ((public or communty) adj2 (aware$ or promot$ or educat$)).mp.
149. or/130-148
150. Patient Care Team/
151. (psc or primary stroke cent$).tw.
152. (stroke adj3 (service$ or center$ or centre$ or team$)).tw.
153. stroke centre.mp.
154. Intensive Care Units/
155. Hospital Units/
156. or/150-155

157. emergency medical services/
158. Emergency Medicine/
159. (ems or emergency medical services).tw.
160. Emergency Service, Hospital/
161. emergency care/
162. (emergency room or er).tw.
163. emergency treatment/
164. ("911" or "999").tw.
165. Paramedic$.mp.
166. or/157-165
167. clinical protocols/
168. program evaluation/
169. exp patient care planning/
170. (protocol$ or care plan$).mp.
171. ((critical or clinical) adj2 path$).mp.
172. treatment plan$.mp.
173. or/167-172
174. 166 and 173
175. RANDOMIZED CONTROLLED TRIAL.pt.
176. CONTROLLED CLINICAL TRIAL.pt.
177. RANDOMIZED CONTROLLED TRIALS.sh.
178. RANDOM ALLOCATION.sh.
179. DOUBLE BLIND METHOD.sh.
180. SINGLE-BLIND METHOD.sh.
181. or/175-180
182. (ANIMALS not HUMAN).sh.
183. 181 not 182
184. CLINICAL TRIAL.pt.
185. exp CLINICAL TRIALS/
186. (clin$ adj25 trial$).ti,ab.
187. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
188. PLACEBOS.sh.
189. placebo$.ti,ab.
190. random$.ti,ab.
191. versus.tw.
192. RESEARCH DESIGN.sh.
193. or/184-192
194. 193 not 182
195. 194 not 183
196. 183 or 195
197. 44 and 196
198. 61 and 196
199. 81 and 7 and 196
200. 89 and 10 and 196
201. 100 and 7 and 196
202. 112 and 7 and 196
203. 129 and 7
204. 149 and 10
205. 156 and 10 and 196
206. 174 and 10
207. or/197,199-203
208. limit 207 to all adult <19 plus years>
209. or/198,204-206
210. or/208-209

Appendix B. Correspondence to Targeted Trial Investigators

October 1, 2004

Dear Dr. _____,

I am writing on behalf of the University of Ottawa's Evidence-based Practice Center (UO-EPC). We are conducting a systematic review on *Acute Stroke, Evaluation & Treatment* under the clinical leadership of Dr. Mukul Sharma. This review is being conducted under a contract from the Agency for Healthcare Research and Quality (AHRQ).

The task involves the following three objectives:

- To determine what interventions for acute stroke (delivered within the first 24 hours from onset of symptoms) are effective in reducing stroke-related morbidity or mortality.
- To review how the safety and effectiveness of these interventions vary with the timing of intervention in relation to onset of symptoms.
- To determine what is the evidence that specific systems of care (i.e., dedicated stroke programs) improve outcomes of acute stroke.

We are seeking out principle investigators, such as you, for additional evidence including unpublished trials that may have been terminated early, in event these trials may yield some valuable data pertinent to our review. We understand that permission would be required to cite any information provided to us and introduced into the public domain.

We look forward to receiving any information you would deem appropriate for inclusion in this review at your earliest convenience.

Kind regards,

Chantelle Garritty, on behalf of Dr. Mukul Sharma & the University of Ottawa Evidence-based Practice Center (UO-EPC)

Appendix C. Data Assessment and Data Abstraction Forms

Relevance Assessment Forms

Level 1 Screening of Titles and Abstracts—Eligibility Criteria

Inclusion Criteria

1. Does this report describe a study involving human participants?
- Yes
- No
- Can't tell

2. Does this study include adults (>16 years old) with Acute Stroke (i.e., intracerebral hemorrhage [ICH] or ischemic stroke [IS])?
- Yes
- No
- Can't tell

3. Is the purpose of the study to investigate the effect (e.g., efficacy, effectiveness, mortality, adverse events) of the following interventions:
a) surgery for ICH, or
b) antihypertensive therapy for ICH, or
c) intra-arterial thrombolytic therapy for IS, or
d) normalization of blood glucose levels for IS, or
e) mechanical clot disruption for IS, or
f) timing of thrombolytic therapy in IS, or
g) pretreatment CT scoring system for IS, or
h) pretreatment MRI scoring system for IS, or
i) CT perfusion/angiography for IS, or
j) community education programs for acute stroke, or
k) use of designated centers for acute stroke, or
l) use of ER protocols for management of acute stroke?
- Yes
- No
- Can't tell

Exclusion Criteria

4. If this is a narrative or systematic review opinion piece or editorial, letter, guideline or policy paper, etc., does it exclusively describe studies already reported elsewhere (i.e., it does not present any empirical evidence published for the first time)?
- Yes

- No
- Can't tell

5. Is this study reported in English?
- Yes
- No
- Can't tell

6. Comments:

Level 2 Screening of Full Articles—Eligibility Criteria

Inclusion Criteria

1. Is this study reported in English?
- Yes
- No

2. Does this report describe a study involving human participants?
- Yes
- No
- Can't tell

3. Does this study include adults (>16 years old) with Acute Stroke (i.e., intracerebral hemorrhage [ICH] or ischemic stroke [IS])?
- Yes
- No
- Can't tell

4. Is the purpose of the study to investigate the effect (e.g., efficacy, effectiveness, mortality, adverse events) of the following interventions:
a) Surgery for ICH, or
b) Antihypertensive therapy for ICH, or
c) Intra-arterial thrombolytic therapy for IS, or
d) Normalization of blood glucose levels for IS, or
e) Mechanical clot disruption for IS, or
f) Timing of thrombolytic therapy in IS, or
g) Pretreatment CT scoring system for IS, or
h) Pretreatment MRI scoring system for IS, or
i) CT perfusion/angiography for IS, or
j) Community education programs for acute stroke, or
k) Use of designated centers for acute stroke, or
l) Use of ER protocols for management of acute stroke?
- Yes
- No
- Can't tell

5. To which of the following topics does this study belong?

(Check all that apply)

- a) Surgery for ICH
- b) Antihypertensive therapy for ICH
- c) Intra-arterial thrombolytic therapy for IS
- d) Normalization of blood glucose levels for IS
- e) Mechanical clot disruption for IS
- f) Timing of thrombolytic therapy in IS
- g) Pretreatment CT scoring system for IS
- h) Pretreatment MRI scoring system for IS
- i) CT perfusion/angiography for IS
- j) Community education programs for acute stroke
- k) Use of designated centers for acute stroke
- l) Use of ER protocols for management of acute stroke

Exclusion Criteria

6. Is this study one of the following?

- Narrative review, or
- Systematic review, or
- Opinion piece, or
- Editorial, or
- Letter, or
- Guideline, or
- Policy paper etc.

- Yes
- No
- Can't tell

7. If answer to the above question is YES, does this article report original research data? (i.e., presents any empirical evidence published for the first time)

- Yes
- No
- Can't tell

8. Was this full reference available by the stop date for relevance assessment at Level II?

- unable to obtain for review by inclusion deadline
- able to obtain for review by inclusion deadline

9. Comments

Study Type Classification

1. Does this report belong to the following Levels of Evidence (see below)?

- yes
- no

2. Level of Evidence of this report (*select one*)
    -RCT parallel design
    -RCT crossover design
    -RCT factorial design
    -Controlled clinical trial (non-RCT)
    -Multiple prospective cohorts
    -At least one prospective cohort & one retrospective cohort
    -Case-control
    -Cross-sectional
    -Before-after (pre-post)
    -Single prospective cohort
    -Single retrospective cohort
    -Case series (noncomparative)
    -Case study
    -Sequential
    -Cross-national ecological analysis
    -Other:

Data Abstraction Forms

General Stroke Data Extraction

1. Initials of reviewer:
2. Reference identification # (Refid):
3. Author, Year, Location [number of sites]:
4. Number of unique studies that this report describes:
5. If other included reports refer to this same study, provide the Refid(s):
6. Publication status (*select one*):
    - Journal publication
    - Grey Literature (e.g., conference paper/abstract, internet document, Book chapter, thesis, etc)
    - Other
7. Funding source type (*select all that apply*):
    - Government (Specify)
    - Industry (Specify)
    - Private (non-industry) (Specify)
    - Hospital (Specify)
    - Other (Specify)
    - Not reported
8. Total # of individuals screened:
9. Full sample size (enrolled in study):
10. Full sample size (completing study):
11. Full sample's percentage of male participants:
12. Comments, including notable differences between study arms / cohorts re '% male participants':
13. Mean age (SD/SE; range) of all study participants:
14. Comments, including notable differences between study arms/cohorts re age:
15. From which racial groups were participants drawn (*select all that apply)?*

- Black/African ancestry
- Native North American
- Hispanic
- Asian
- Caucasian/European
- Other (specify)
- Not reported
- Can't tell

16. Specify each racial group's percentage/proportion of full sample:
17. Comments, including notable differences between study arms/cohorts re racial composition**:**
18. Specify each socioeconomic status (i.e., employment status, insurance, income, education, married) group's percentage/proportion of full sample:
19. Comments, including notable differences between study arms/cohorts re socioeconomic status**:**
20. Eligibility criteria (*select all*):
    - List of study's inclusion criteria:
    - List of study's exclusion criteria:
21. Type of setting where study was conducted (e.g., Emergency room, Teaching Hospital, etc):
22. Adverse events/ side effects reported in the present, per study arm/cohort:
23. Number of drop outs/withdrawals, per study arm/cohort:
24. Study duration, including units (includes run-in period duration, washout duration, intervention length, etc.):
25. Comment box (*optional*):

Specific Acute Stroke Data Extraction

1. Initials of reviewer:
2. Reference identification # (Refid):
3. Author, Year, Location [number of sites]:
4. Number of unique studies that this report describes:
5. If other included reports refer to this same study, provide the Refid(s):
6. How was acute stroke defined?
7. How was acute stroke diagnosed?
8. How was Acute Stroke classified (e.g. Ischemic, Hemorrhagic)?
9. How was the severity of Acute Stroke defined?
10. Describe the full sample's baseline level of Acute Stroke symptoms and/or signs severity:
11. Comments, including notable differences between arms/cohorts re participants' baseline level of Acute Stroke symptoms and/or signs severity:
12. Time since Stroke onset to intervention (specify: mean; range):
13. Comments, including notable differences between arms/cohorts re participants' baseline disease duration:
14. Pre-study medication(s) or treatments for Acute Stroke, including dose/ frequency:
15. Concurrent/antecedent conditions (*select all that apply*)
    - Arterial Hypertension
    - Diabetes Mellitus
    - Dyslipidemia
    - Smoking
    - Other
    - Not Reported

16. Specify the percentage/proportion of the whole sample re each type of each concurrent/antecedent condition:
17. Comments, including notable differences between study arms/cohorts re concurrent/antecedent conditions:
18. Specify pre-study medications or treatments for each concurrent/antecedent condition, with dose/frequency:
19. Comments, including notable differences between study arms/cohorts re pre-study medications/treatments:
20. Which question(s) this study answer (*select all that apply*):

- (A) Surgery for ICH
- (B) Antihypertensive therapy for ICH
- (C) Intra-arterial thrombolytic therapy for IS
- (D) Normalization of blood glucose levels for IS
- (E) Mechanical clot disruption for IS
- (F) Timing of Thrombolytic therapy for IS
- (G) Pretreatment CT scoring system for IS
- (H) Pretreatment MRI scoring system for IS
- (I) CT perfusion/angiography for IS
- (J) Community education programs for acute stroke
- (K) Use of designated centres for acute stroke
- (L) Use of ER protocols for management of acute stroke

21. Participants were enrolled according to which criterion (*select one*)?

- Intention-to-treat (all randomized/enrolled)
- Those receiving at least one dose
- Those completing the study (i.e., with follow-up data)
- Can't tell
- Not applicable
- Other:

22. Cointerventions: Medications and/or treatments allowed or permitted during the study period:
23. Comments, including notable differences between study arms/cohorts re on-study medications/treatments:
24. Type of intervention (*Select one if applicable*)
Answer for Interventions
(B) Antihypertensive Therapy for ICH &/or
(D) Normalization of blood glucose levels for IS

- Drug (see below)
- Target (give target i.e., blood pressure, glucose level)
- Not applicable

25. Imaging tests performed on-study: (*check all that apply*)
Answer for Interventions
(G) Pretreatment CT scoring system for IS,
(H) Pretreatment MRI scoring system for IS, &/or
(I) CT perfusion/angiography for IS

- CT
- CT perfusion
- CT angio
- MRI (other than DWI/PWI)
- MRI DWI/PWI
- Other
- Not reported
- Not applicable

26. Describe listed characteristics of imaging tests (see above question) used to make the intervention decision.
Answer for Interventions
(G) Pretreatment CT scoring system for IS,
(H) Pretreatment MRI scoring system for IS, &/or
(I) CT perfusion/angiography for IS
27. 'Centre' definition used: (*select all that apply*)
Answer for Intervention
(K) Use of designated centres for acute stroke
- Brain Attack Coalition (BAC) (definition at bottom)
- Other (describe)

28. Intervention components (check all that apply)
Answer for Intervention
(L) Use of ER protocols for management of acute stroke
- Stroke team
- 24 hour CT
- Written protocol orders
- Professional education
- Drug storage in ER
- Other

29. Study **GROUP 1:** Intervention of interest (e.g., Surgery for ICH): (*Select all*)
- Define study group (e.g., by time window since stroke onset):
- Intervention/ exposure/ procedure type:
- Dose/ frequency/ timing (if apply):
- Intervention Length:
- N enrolled/completed:

30. Study **GROUP 2:** first comparator (e.g., placebo, other type of intervention): (Select all):
- Define study group (e.g., by time window since stroke onset):
- Intervention/ exposure/ procedure type:
- Dose/ frequency/ timing (if apply):
- Intervention Length:
- N enrolled/completed:

31. Study **GROUP 3:** (if applicable)
- Define study group (e.g., by time window since stroke onset):
- Intervention/ exposure/ procedure type:
- Dose/ frequency/ timing (if apply):
- Intervention Length:
- N enrolled/completed:

32. Study **GROUP 4:** (if applicable)
- Define study group (e.g., by time window since stroke onset):
- Intervention/ exposure/ procedure type:
- Dose/ frequency/ timing (if apply):
- Intervention Length:
- N enrolled/completed:

33. Outcome measures with significance (e.g., Surgery S better than no surgery)
(*select all that apply*)
- NIHSS
- mRS (Modified Rankin Scale)
- Barthel
- FIM
- Time to treatment

- Time to presentation to ER (arrival)
- Other (describe all the outcomes assessed not mentioned above)

34. Identify any problems with the research design (e.g., definition of placebo/control(s); inappropriateness of run-in and washout periods), or its implementation:
35. Comment box (*optional):*

Quality Assessment Forms—RCTs

Jadad Scale

Descriptor			**Yes**	**No**
Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?				
The method used to generate the sequence of randomization was described and it was **appropriate** (table of random numbers, computer generated, etc)				
Was the report of allocation concealment:	Adequate ☐	Inadequate ☐	Unclear ☐	
Was the study described as double blind?				
The method of double blinding was described and it was **appropriate** (identical placebo, active placebo, dummy, etc)?				
Was there a description of withdrawals and dropouts?				

Note: Clinical controlled trials were assessed out of a possible score of 3 according to a modified Jadad scale

Allocation Concealment - Refers to the technique used to implement the randomization sequence, not to generate it.

Adequate • Sequentially numbered, opaque, sealed envelopes (SNOSE) • Pharmacy controlled • Numbered or ordered containers • Central randomization – for example by telephone to a trials office or other method whose description contained elements convincing of concealment – for example a secure computer assisted method.
Inadequate • Alternation • Reference to case record numbers or to dates of birth

Unclear

- No mention of an allocation concealment approach at all
- An approach that does not fall into either adequate or inadequate allocation concealment

Quality Assessment Forms—Case-Control and Cohort Studies

Newcastle-Ottawa Scale (NOS)

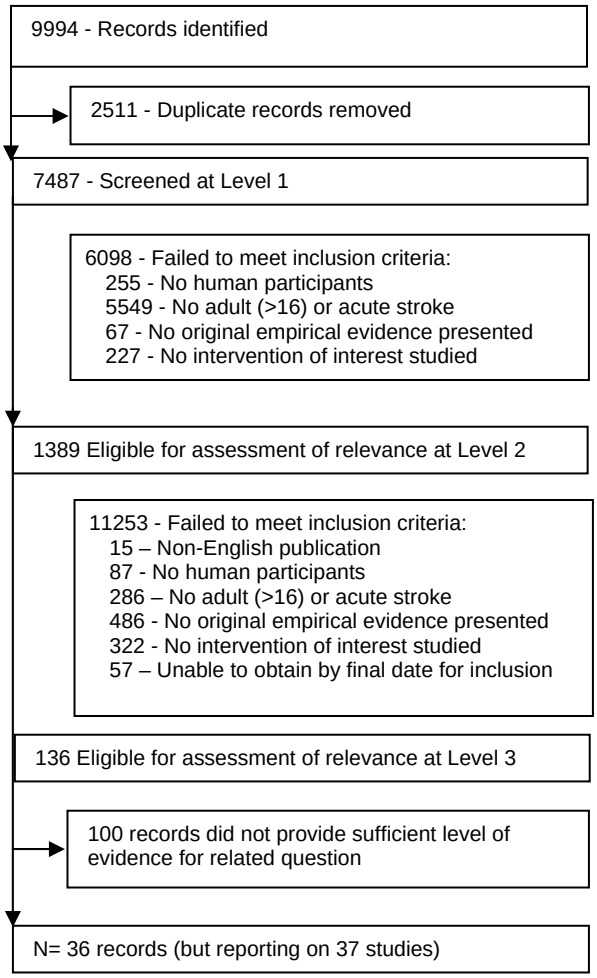
Descriptor	Yes	No	Can't tell
Was the therapeutic intervention reported?			
Were the inclusion/exclusion criteria reported?			
Was follow-up reported as an inclusion criterion?			
Was the sample size determination reported (cases accrued consecutively or non consecutively over a specified time period)?			
Were the sample size calculations (and any assumptions) reported?			
Was the time period for accrual of cases and whether they were accumulated prospectively or retrospectively reported?			
Were the sources of participants (same or different clinicians, one or more center) reported?			
Were how the outcome assessments made and who made them reported?			
Was blinding reported?			
Were the primary and secondary measures reported?			
Was the timing of the outcome measures reported?			
Was a follow-up schedule reported?			
Were efforts used to maintain follow-up with participants reported?			
Did the authors report on compliance with follow-up?			
Was the method of data collection reported?			
Were any participant exclusions from data analysis reported?			
Was the statistical approach for analyzing the data reported?			
Did the authors report any missing data and how it was handled in the data analysis?			
Did the authors report any adverse events?			

Quality Assessment Forms—Noncomparative Case-Series Studies

Quality assessment	Yes	Partial	No	N/A
1. Question / objective sufficiently described?				
2. Design evident and appropriate to answer study question?				
3. Subject characteristics sufficiently described?				
4. Subjects appropriate to the study question?				
5. Controls used and appropriate? **(if no control, check no)**				
6. Method of subject selection described and appropriate?				
7. If random allocation to treatment groups was possible, is it described? (if not possible, check n/a)				
8. If blinding of investigators to intervention was possible, is it reported? (If not possible, n/a)				
9. If blinding of subjects to intervention was possible, is it reported? (If not possible, n/a)[1]				
10. Outcome measure well defined and robust to measurement bias? Means of assessment reported?				
11. Confounding accounted for?				
12. Sample size adequate?				
13. Post hoc power calculations or confidence intervals reported for statistically non-significant results?				
14. Statistical analyses appropriate?				
15. Statistical tests stated?				
16. Exact p-values or confidence intervals stated?				
17. Attrition of subjects and reason for attrition recorded?				
18. Results reported in sufficient detail?				
19. Do the results support the conclusions?				
Sum (items 1-19)				

Appendix D. Modified QUOROM Flow Chart

Modified QUOROM Flow Chart



*Note: some items were eligible for both reviews, therefore, the sum does not add up to the number of included studies.

Appendix E. Evidence Tables

Experimental Studies

Evidence Table 1: Randomized clinical trials

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Albers, 2002, US[1] Design: RCT Parallel	n= 61 Age: IG 66 (10)y; CG; 66 (11)y % Male: IG 82.6; CG 57.9 Race: White IG 95.7%; CG 84.2%e; Black IG 0%; CG 10.5%; Hispanic IG 0%; CG 5.3%; Asian IG 4.3%; CG 0% Inclusion Criteria: Acute IS defined by sudden onset of an acute focal neurological deficit due to ischemia with no sign of hemorrhage by CT; MCA origin with measurable focal neurological deficit; age 18-79y; within 3-5 hr post onset Exclusion Criteria: ICH by CT; sign of ischemia in > 1/3 of the territory of MCA; other exclusion as ATLANTIS A trial[2]	I: Timing of thrombolytic therapy in IS (n=23) C: Control (n=38)	I: tPA / 0.9 mg/kg C: Placebo	• Mortality (90 d) • NIHSS, mRS, BI, GCS (30, 90d) • Rate of ICH	1/5	Genentech, Inc.

US = United States; RCT = randomized controlled trial; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated

Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Alexandrov, 2004, US & Canada[3] Design: RCT Parallel	n=126 Age: IG 67(12)y; CG 70(13)y % Male: NR Race: NR Inclusion Criteria: Acute IS of MCA, within 3 hr post onset; IG Abnormal flow through MCA, with TIBI scale grade 0-3 (Thrombolysis in Brain Ischemia flow-grading system) before TPA tx Exclusion Criteria: NR	I: Mechanical clot disruption for IS (n=63) C: Control (n=63)	I: Continuous 2-MHz transcranial Doppler ultrasonography / 750 mW & 3-6 mm insonation for 2hr + tPA/ 0.9 mg/kg, up to 90 mg/ within 3 hr post onset C: tPA/ same as IG + placebo (inactive channel with no continuous insonation)	• Complete recanalization rate • Clinical recovery	4/5	US sites by NINDS grants & Canadian sites by the Canadian Institutes of Health Research & the Alberta Heritage Foundation

US = United States; RCT = randomized controlled trial; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Auer, 1989, Austria[4] Design: RCT Parallel	n=100 Age: 30-80y % Male: IG 56; CG 66 Race: NR Inclusion Criteria: Acute, hematoma > 10 cm^3; within 48 hr of hemorrhage with neurological deficits, consciousness impairment, approved for surgery / angiography, Exclusion Criteria: aneurysm, arteriovenous malformation, tumor as the bleeding source, post-traumatic intracerebral hematomas	I: Surgery for ICH, (n=50) C: Medical tx (n=50)	I: Hematoma evacuation through burr hole/<24h C: Medical tx, endoscopy	• Mortality rate (1 wk*, 6 mo*) • Neurological recovery by clinical & CT signs (6 wk, 6 mo)	1/5	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Batjer, 1999, US[5] Design: RCT Parallel	n=21 Age: IG 53.3 (3.4)y; CG1 54.9 (3.5) y; CG2 53.3 (5.9) y % Male: NR Race: NR Inclusion Criteria: Acute hypertensive putaminal ICH ≥3cm in diameter, moderate to severe hemiparesis/ uniform hemiplegia (grade 1-3)< 24hr post onset Exclusion Criteria: Un-associated neurologic illness, end-stage systemic disease; coagulopathy of any cause; aneurysm; arterioveous malformation, or tumour; decorticate or decerebrate posturing	I: Surgery for ICH (n=8) C1: Best medical management (n=9) C2: Best medical management + intracranial pressure monitoring (n=4)	I: Frontotemporal or pterional craniotomy C1: IV dexamethasone/ 4mg tapered over 7-14 d C2: Antihypertensive same as C1 arm + placement of frontal ventriculostomy	• Mortality rate (6 mo) • Functional recovery (6 mo)	1/5	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Clark, 1999, US[6] Design: RCT Parallel	n= 547 Age: IG: 66 (12)y; CG; 65 (11)y % Male: IG: 54.8; CG: 63.6 Race: White IG: 84.6%; CG: 83.6% Inclusion Criteria: Acute IS defined by sudden onset of an acute focal neurological deficit due to ischemia with no sign of hemorrhage by CT; MCA origin with measurable focal neurological deficit; age 18-79y; within 3-5 hr post onset Exclusion Criteria: ICH by CT; sign of ischemia in > 1/3 of the territory of MCA; other exclusion as ATLANTIS A trial[2]	I: Timing of thrombolytic therapy in IS (n=272) C: Control (n=275)	I: TPA / 0.9 mg/kg, up to 90 mg (10% IV bolus over 1-2 min & 90% IV infusion over 1 hr)/ 1 hr C: Placebo/ matching dose for 1 hr	• Mortality (90 d) • NIHSS, mRS, BI, GCS (30, 90d)	2/5	Genentech, Inc.

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Clark, 2000, US[2] Design: RCT Parallel	n=142 Age: I 67 (13)y; C 65 (12)y % Male: NR Race: I = 82% White; C = 86% White Inclusion Criteria: Acute stroke with neurological deficit, within 6 hr post symptom onset Exclusion Criteria: Coma, severe obtundation, fixed eye deviation, complete hemiplegia; NIHSS <4; seizure; known ICH; hypertension; septic embolus; pericarditis or ventricular thrombus or aneurysm; trauma within 30 d; head trauma within 90 d; diathesis; pregnancy, lactation or parturition within 30 d; glucose <50 or >400, platelets <100,000, hematocrit <25; terminal illness; S hazard to tx	I: Timing of thrombolytic therapy in IS (n=71) C: Control (n=71)	I: TPA / 0.9 mg/kg, up to 90 mg (10% IV bolus over 1-2 min & 90% IV infusion over 1 hr)/ 1 hr C: Placebo/ matching dose for 1 hr	• Recanalization* (negative effect of TPA) • NIHSS, mRS, Barthel Index • Mortality (90 d) • Symptomatic ICH rate	2/5	Genentech, Inc.

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment

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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
del Zoppo, 1998, US & Canada[7] Design: RCT parallel	n=40 Age: full 64.2 (12.1)y; IG 66.5 (11)y, CG 69.6 (11.1)y % Male: IG 54; CG 36 Race: White IG 77%; CG 71% Inclusion Criteria: Acute carotid artery stroke; new focal neurological signs in the MCA within 6 hr of onset, NIHSS score ≥4; (except for isolated aphasia or hemianopsia; age 18-85y Exclusion Criteria: NIHSS score >30; coma; minor stroke symptoms; history of stroke within 6 wk; seizure; hypertension; head trauma within 90 d; active or recent hemorrhage within 14 d; diathesis; oral anticoagulation international normalized ratio >1.5	I: Timing of thrombolytic therapy in IS (n=26) C: Placebo (n=14)	I: IA Pro-Urokinase/ 6 mg + Heparin/ 100 IU/kg bolus + 1000-2000 I.U./hr infusion/ median 5.5 hr post symptom onset C: Saline placebo/ matching heparin/ matching time	• MCA recanalization* • Hemorrhage frequencies • Mortality • Functional outcomes (mRS, Barthel Index, NIHSS)	3/5	Abbott Laboratories

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment

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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Eggers, 2003, Germany[8] Design: RCT Parallel	n=25 Age: full 61.3 (9.1)y; IG 60.3 (10.3)y; CG 62.1 (8.3)y % Male: full 76; IG 73; CG 79 Race: NR Inclusion Criteria: Acute IS in MCA/ M1; 18-80y, within 3 hr symptom onset (according to NINDS criteria) Exclusion Criteria: age <18y; pregnancy or lactation; insufficient acoustic window no allowing identification of the main basal cerebral arteries	I: Mechanical clot disruption for IS (n=11) C: Control (n=14)	I: Ultrasound/ continues 2 MHz transcranial Doppler mode + TPA/ 0.9 mg/kg IV over 1 hr C: Matching IV TPA tx for 1 hr	• Barthel Index (90 d)* • NIHSS/ mRS • Mortality	1/5	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Furlan, 1999, US & Canada[9] Design: RCT parallel	n=180 Age: full 64 (14)y (groups identical in age) % Male: full 59; IG 58, CG 61 Race: White 80% Inclusion Criteria: Acute IS (MCA), 18-85y, with new neurological symptoms < 6 hr post symptom onset; NIHSS score ≥4 Exclusion Criteria: NIHSS score >30; coma; improving neurological signs; history of stroke; seizure at onset; subarachnoid hemorrhage; history of ICH; neoplasm or subarachnoid hemorrhage; septic embolism; lacunar stroke; surgery; organ biopsy; head trauma within 90 d; active or recent hemorrhage within 30 d; known hemorrhagic diathesis; uncontrolled hypertension	I: Timing of thrombolytic therapy in IS: IA Urokinase tx (n=121) C: Placebo (n=59)	I: IA Urokinase/ 9 mg + heparin/NR for 2 hr C: Saline + Heparin for 2 hr	• mRS (90 d) • MCA recanalization* • Frequency of ICH • Mortality (90 d)	3/5	Abbott Laboratories

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment

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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Gray, 2004 UK[10] Design: RCT Parallel	n=452 Age: IG 75.2y; CG 74.4y % Male: IG 50.6; CG 54.1 Race: NR Inclusion Criteria: Acute stroke< 24 hr post symptom onset, with admission glucose level >6 to <17 mmol/L Exclusion Criteria: Coma; hx of insulin-requiring diabetes; anemia; renal failure; congestive heart failure; S pre-existing disability	I: Normalization of blood glucose levels for IS (n=221) C: Control (n=231)	I: (GKI) Dextrose / continuous IV of 10% + Potassium chloride /20 mmol + Human soluble Actrapid / variable dose starting with 16 U/L for 24 hr C: Saline/ 0.9% at 100 mL/hr for 24 hr	• Difference in mean plasma glucose values at subsequent time intervals in 24 h	1/5	NHS Northern & Yorkshire Research & Development Directorate; PPP Foundation

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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Hacke, 1998, Europe, Austrialia, New Zealanc[11] Design: RCT Parallel	n=800 Age: median, IG=CG 68 y % Male: IG 60.6; CG 56.2 Race: NR Inclusion Criteria: Acute ischemic stroke within 6 hrs of onset, early infarct change on CT less than 33% of the MCA territory Exclusion Criteria: signs of ICH or parenchymal hypoattenuation > 1/3 MCA territory; brain swelling > 33% of MCA; subarachnoid haemorrhage; unknown time of onset; coma or stupor; hemiplegia + fixed eye deviation; minor stroke symptoms (> 50 of the maximum 58 points on the SSS before randomization, or rapid improvement of symptoms); seizure < 6 mo; hypertension at randomization; traumatic brain injury < 14 d; recent surgery on the central nervous system; gastrointestinal or urinary tract haemorrhage; current tx with IA or subcutaneous heparin to raise the clotting time; known hereditary or acquired haemorrhagic diathesis; lactation; pregnancy or recent parturition < 30 d; lack of medically approved means of concentrations	I: rtPA (n=409) C: Placebo (n=391)	I: Alteplase 0.9 mg/kg bodyweight, maximum of 90 mg/pts; bolus of 10% of the total dose over 1-2 min followed by a 60 min IV infusion of the remaining dose. (admin of anticoagulants, antiplatelet agents, haemorrheological agents, potential neuro-protective drugs & volume expanders were prohibited during 1st 24 hr) C: Identical tx with placebo agent	• Mortality • mRS • ICH rate	4/5	NR

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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Hacke, 1995, Europe [12] Design: RCT Parallel	n=620 Age: IG 65 (12)y; CG 65 (11) % Male: IG 60.1; CG 65.5 Race: NR Inclusion Criteria: Acute ischemic stroke, 18-80 y; 0-6 hrs, early infarct change on CT less than 33% of the MCA territory Exclusion Criteria: See the eligibility criteria listed for Hacke 1998[11]	I: rtPA (n=313) C: Placebo (n=307)	I: rtPA 1.1 mg/kg C: Placebo	• Primary: Barthel, mRS (90 d) • Secondary: Combined Barthel & mRS, SSS (90 d)/ Mortality (30 d) • Tertiary: Early neurological recovery (SSS), and duration of hospital stay	4/5	Sponsored by Dr Karl Thomae GmbH (a member of Boehringer Ingelheim, Biberach, Germany)

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment

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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Haley, 1993, US[13] Design: RCT Parallel	n=27 Age: Within 90 min: IG 65 (11)y; CG 64 (8) y; 91-180 min: IG 72 (1)y, CG 67 (9)y % Male: NR Race: NR Inclusion Criteria: Acute IS causing neurological deficit, age 18-80, within 90 min or 91-180 min post symptom onset Exclusion Criteria: Mild stroke; symptoms only of sensory loss or ataxia; IC or subarachnoid hemorrhage; pregnancy, lactation; platelet < 100 000/mm3; protrombin time >15 s; elevated partial thromboplastin time due to heparin tx; major surgery or serious trauma within 14 d; gastrointestinal or urinary tract hemorrhage within 21d; arterial puncture at noncompressible site within 7 d; mean BP ≥135 mmHg; brain infarction within 90 d; serious medical illness	I: Timing of thrombolytic therapy in IS (n=14) C: Control (n=13)	I: IV tPA / 0.85 mg/kg for 1 hr C: IV placebo/ matching dose for 1 hr	• NIHSS (baseline, 30 min, 1, 2 hr post infusion & 24 hr* post stroke), mRS, Barthel Index, GCS • Mortality • Onset to treatment time (OTT) interaction	5/5	Genentech Inc.

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment

NOTE: Numerical values are mean (standard deviation) unless otherwise indicated

Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Juvela, 1989, Finland{1124} Design: RCT Parallel	n=52 Age: IG 54 (8.9)y, CG 49.3 (10.1)y % Male: full 58; IG 65; CG 50 Race: NR Inclusion Criteria: Acute ICH within 24 hr post bleed; unconscious &/or severe hemiparesis or dysphasia Exclusion Criteria: Cerebellar hematomas; traumatic hemorrhages; hemorrhages into brain tumors, & hemorrhages from cerebral aneurysms & arteriovenous malformations; malignant diseases; severe heart, lung or endocrine diseases; improving clinical condition or no reaction to pain	I: Surgery for ICH (n=26) C: Conservative tx (n=26)	I: Surgery within 48 hr post bleeding (methods NR) C1: NR/ within 48 hr post bleeding	• Mortality rate (6 mo) • Morbidity • GCS	1/5	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Kase, 2001, US[14] Design: RCT Parallel	n=174 Age: 64.2 (12.1)y % Male: NR Race: NR Inclusion Criteria: Acute IS M1 or M2 segments of MCA <6 hr post symptom onset; NIHSS score 4-30 Exclusion Criteria: NR	I: Timing of thrombolytic therapy in IS (n=110) C: Placebo (n=64)	I: IA Urokinase/ 9 mg directly into clot for 2 hr + Heparin/2000 IU bolus followed by 500 IU/hr for 2 hr C: Saline + Heparin/ matching dose & timing	• Symptomatic ICH (relationship with baseline characteristics) • Mortality following symptomatic ICH • Serum glucose level	2/5	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Keris, 2001, Latvia[15] Design: RCT Parallel	n=45 Age: IG 53 (9)y; CG 65 (8)y % Male: IG 83; CG 51.5 Race: NR Inclusion Criteria: Acute severe hemiparetic IS within 6 hr post symptom onset Exclusion Criteria: sulcal effacement, mass effect, edema, or possible hemorrhage on CT	I: Timing of thrombolytic therapy in IS (n=12) C: Conventional tx (n=33)	I: IA TPA/ 25 mg for 5-10 min; IV TPA/25 mg for 60 min + Heparin/ 5000 U initially & twice a day for several days C: Heparin/ matching dose & frequency	• mRS (1, 12 mo, rated as good/poor) • Mortality	1/5	Supported in part by Medical Academy of Latvia

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Lewandowski, 1999, US[16] Design: RCT Parallel	n=35 Age: IG 65.6 (11.2)y; CG 67.3 (12.3)y % Male: full 54.3; IG 53; CG 56 Race: White, full 48.6%; IG 41%; CG 56% Inclusion Criteria: Acute focal IS within 3 hr of symptom onset (based on NINDS TPA stroke study) Exclusion Criteria: based on NINDS tPA stroke study, also excluded pts with hx of stroke within 6 wk; surgery biopsy or haemorrhage within 30 d of randomization	I: Timing of thrombolytic therapy in IS (n=17) C: Placebo+ IA thrombolytic tx (n=18)	I: IV TPA/ 0.6 mg/kg for 30 min; IA TPA/ 0.6 mg/kg max 20 mg for max 2 hr C: IV placebo + IA TPA/ matching dose for 2 hr max	• NIHSS (7-10 d) • Barthel Index, mRS, GCS (3mo) • ICH & recanalization rate	4/5	Genetech, Inc

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Marler, 2000, US[17] (Part A) Design: RCT Parallel	n=302 Age: NR % Male: NR Race: NR Inclusion Criteria: Acute stroke 0-90 min post symptom onset (based on NINDS TPA study for stroke) Exclusion Criteria: based on NINDS TPA study for stroke	I: Timing of thrombolytic therapy in IS (n=157) C: Control (n=145)	I: IV TPA/ 0.9 mg/kg (10% bolus & 90% as infusion), max 90 mg, for 1 hr C: Placebo powder/ 0.9 mg/kg 10% bolus & 90% as IV infusion for 1 hr	• NIHSS mRS, Barthel Index, GCS (baseline, 24 hr, 3 mo) • Time to tx & outcome	1/5	NINDS; Genetech Inc.

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Marler, 2000, US[17] Part B Design: RCT Parallel	n=320 Age: NR % Male: NR Race: NR Inclusion Criteria: Acute stroke 91-180 min post symptom onset (based on NINDS TPA study for stroke) Exclusion Criteria: based on NINDS TPA study for stroke	I: Timing of thrombolytic therapy in IS (n=153) C: Control (n=167)	I: IV TPA/ 0.9 mg/kg (10% bolus & 90% as infusion), max 90 mg, for 1 hr C: Placebo powder/ 0.9 mg/kg 10% bolus & 90% as IV infusion for 1 hr	• NIHSS, mRS, Barthel Index, GCS (baseline, 24 hr, 3 mo), • Time to tx & outcome	1/5	NINDS; Genetech Inc.

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Mendelow, 2005, UK[18] Design: RCT Parallel (Reviewer nominated; published beyond search dates)	n=1033 Age: IG 62 (52-70)y; CG 62 (53-71)y % male: full 57.2; IG 57; 58CG Race: NR Inclusion Criteria: CT evidence of spontaneous supratentorial ICH, within 72 hr; uncertainty by neurosurgeon about benefits of either tx; hematoma ≥ 2 cm; GCS >=5 Exclusion Criteria: haemorrhage due to an aneurysm or an angiographically proven arterobenous malformation; haemorrhage secondary ot a tumour or trauma; pts with cerebellar haemorrhage or extension of a supratentorial haelorrhage intor the brainstem; pts with severe pre-existing physical or mental diability or severe comorbidity that might intrerfer with the assessment of outcome;or if the surgery could not be undertaken within 24 hr of randomization	I: Surgery for ICH (n=503) C: Conservative tx (n=530) Baseline differences: NR Comments: Cross over from IG to CG n=31; from CG to IG n=140	I: Early surgery combined haematoma evacuation within 24 hr of randomization C: Medical tx followed by evacuation if necessary	• Mortality • Functional outcomes (BI, mRS)	3/5	MRC (UK), the Stroke Association (UK), & the Northern Brainwave Appeal

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Morgenstern, 1998, US[19] Design: RCT Parallel	n=34 Age: IG 56 (22-72) y; CG 51 (37-77) y % Male: full 65; IG 29.4; CG 41 Race: 32.4 % non-White, 67.6% White Inclusion Criteria: Acute ICH > 9 mL diagnosed by CT within 3 hr screening, <12 hr; GCS 5-15 Exclusion Criteria: Secondary ICH; brainstem or cerebellar ICH, or ICH of thalamus or ventricular system; pre-hemorrhage low functional level; coagulopathy (>15 s; elevated partial thromboplastin time, platelet <100,000/mm^3); precluded 6 mo survival; biopsy-proved amyloid angiopathy; hematoma volume 10-19 mL; GCS >15; better than antigravity strength on the affected side; ventricular extension >1/2 of one lateral ventricle or 1/3 of both lateral ventricles	I: Surgery for ICH (n=17) C: Standard medical tx (n=17)	I: Open craniotomy & hematoma evacuation/ <12 hr post onset C1: Standard medical tx /NR	• Mortality • Barthel Index, GCS	1/5	AHA Clinician-Scientist Award (L.B.M.)

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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Patel, 2001, US[20] Design: RCT Parallel	n=624 Age: 61-68y % Male: NR Race: NR Enrolment: Jan 1991–Oct 1994 Inclusion Criteria: Acute IS < 3 hr (0-90 & 91-180 min) post onset Exclusion Criteria: NR	I: Pretreatment CT scoring system for IS (n=312) C: Control (n=312)	I: CT/ within 3h symptom onset + IV tPA C: CT /within 3 hr symptom onset + placebo	• Frequency of EIC on baseline CT/ association of EIC with other baseline variables; effect of EIC on deterioration at 24 hr • NIHSS, Barthel Index, mRS, GCS (3 mo) • Mortality (3 mo) • ICH rate (within 36 hr of tx)	2/5	NINDS - NIH Awards, Genentech Inc.

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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Roberts, 2002, US[21] Design: RCT Parallel	n=159 Age: NR % Male: NR Race: NR Inclusion Criteria: Acute IS of MCA origin within 6 hr of onset; angiography: complete occlusion or contrast penetration with minimal perfusion of M1 or and M2 (based on PROACT II trial criteria segment of MCA) Exclusion Criteria: based on PROACT II trial criteria	I: Pre-tx CT scoring system for IS (n=107) C: Control (n=52)	I: CT, angiography /baseline, 24 hr, 7-10 d + recombinant pro-Urokinase/ 9 mg + IV heparin/2000 U bolus & 500U/hr for 4 hr at beginning of angiography C: CT/ matching intervals + IV heparin/ matching dose	• Correlation of baseline CT with clinical outcomes • NIHSS, mRS (90 d) • Mortality (90 d)	1/5	Abbott Laboratories

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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Scott, 1999, UK[22] Design: RCT Parallel	n=53 Age: median IG 74 (11)y; CG 74 (9.6)y % Male: full 44; IG 52; CG 36 Race: NR Inclusion Criteria: Acute IS with neurological deficit lasting >24 hr, age >18 y; within 24 hr of onset Exclusion Criteria: > 24 hr post onset; coma; pneumonia; heart failure (New York Heart Association grades 3 or 4), renal failure (creatinine level of > 200 micro sing-mol/l; anemia (Hb 3); dementia; isolated posterior circulation syndromes without physical disability; pure language disorders; previously diagnosed insulin treated diabetes (type 1 or 2); or subarachnoid hemorrhage	I: Normalization of blood glucose levels for IS (n=28) C: Control (n=25)	I: (GKI) Dextrose/ 500 mL 10% + Potassium chloride 20 mmol + Human soluble Actrapid insulin/16 U/L C: Same as I/ glucoscans q2h for 24 hr	• Mortality • Plasma glucose level	2/5	Grant from Stroke Association of England & Wales; & a Northern & Yorkshire NHS Regional Training Fellowship

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Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Teernstra, 2003, The Netherlands[23] Design: RCT Parallel	n=71 Age: IG 67 (± 68, range 47-84) y; CG 69 (±71, range 49-89) y % Male: full 56.3; IG 58; CG 56 Race: NR Inclusion Criteria: Pts with expected mortality of 88%; age >45 y, ICH >10 cm^3, within 72 hrs of ictus, Glasgow Eye Motor Score 2-10 Exclusion Criteria: Arterioveous malformation	I: Surgery for ICH (n=36) C: No-Surgery (n=35)	I: Stereotactic tx of ICH by plasminogen activator, Urokinase/ 5000 IU, 8 x in 6 hr intervals over 48 hr C1: Standard medical care	• ICH volume reduction (immediate*) • mRS • Mortality (6mo)	2/5	Grant from the Fund for Developmental Medicine, Health Insurance Executive Board

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated

Evidence Table 1 (cont'd): Randomized clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Jadad)	Funding Source
Zuccarello, 1999, US[24] Design: RCT Parallel	n=20 Age: 62.4 (NR)y, 27-80y % Male: 55 Race: White 60%; Black 40% Inclusion Criteria: Acute supratentorial ICH >10 cm^3, diagnosed by CT, with focal neurological deficit; age >18y; GCS >4, within 24 hr of onset; surgery within 3 hr of randomization Exclusion Criteria: Lack of neurological deficit; infratentorial ICH; vascular abnormality proven by CT; terminal illness; coagulopathy; traumatic ICH; pregnancy	I: Surgery for ICH (n=9) C: Control (n=11)	I: Varied techniques i.e. open craniotomy or CT-guided Stereotactic aspiration with 6000 U Urokinase in 12 hr intervals/ median 8 hr 35 min post onset C: Medical tx/ varied according to tx regiment/ median 3 hr 17 min onset to admission & 3 hr 10 min admission to randomization	• NIHSS (median 3 mo)* • Mortality • Barhel Index • ICH volume	2/5	NINDS

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated

Evidence Table 1 (cont'd): Controlled clinical trial

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes (follow-up interval)	Quality Assessment (Modified Jadad)	Funding Source
Morgenstern, 2003, US[25] Design: Controlled Clinical Trial	n=1427 (for all 3 phases); phase 3 only: n=238 Age: phase 1: >21y % Male: phase 1: IG 42.6, CG 38.2; phase 2: IG 43.3, CG 41.9; phase 3: IG 43.1, CG 43.5 Race: Non-White/ phase 1: IG 23.4%, CG 34%; phase 2: IG 20.8%, CG 28%; phase 3: IG 25.4%, CG 31.5% Inclusion Criteria: County residents experience of cerebrovascular event; IV tPA inclusion according to NINDS Exclusion Criteria: non-résidents; age < 21y	I: Community education program for acute stroke (n=748/ phase 3: n=130) C: Control (n=679/ phase 3: n=108)	I: Community education + professional development & organizational change/ 15 mo C: No intervention/15 mo	• Frequency of IV TPA tx in IS* • Frequency of IV TPA in eligible candidates*	1/3	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated

Observational Studies

Evidence Table 2: Multiple prospective cohort

Study Identification	Population Characteristics	Intervention	Technique /Dose /Timing	Reported Outcomes	Quality Assessment	Funding Source
Suarez, 2002, US[26] Design: Multiple Prospective Cohort	n =45 Age: 67 (13)y % Male: 42 Race: NR Inclusion Criteria: Acute IS <3hrs post symptom onset; no improvement on clinical sign; no ICH on CT; age 18-80; NIHSS score ≥4 Exclusion Criteria: Evidence of cerebral hemorrhage or mass effect on CT; questionable diagnosis (e.g., seizure; high risk hemorrhage; pregnancy or delivery < 14 d; diastolic BP>120 mmHg)	I: Pre-treatment MRI scoring system for IS (n=45)	I: IV TPA/ 0.6 mg/Kg /completed within 5 hr of onset + Emergency MRI (Diffusion weighted & Perfusion weighted) + Angiography in case of acute cortical infarction and when determined with vessel occlusion, IA Urokinase/ up to 750,000 units or IA tPA for maximum 0.3 mg/kg	• Correlation between abnormal perfusion-weighted imaging findings and cerebral angiographic findings • Symptomatic ICH • Mortality • NIHSS, Barthel Index (3 mo post tx)	9/19	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated; TOAST = Trial of Org 10172 in Acute Stroke Treatment

Evidence Table 2 (cont'd): Single retrospective cohort

Study Identification	Population Characteristics	Intervention	Technique /Dose /Timing	Reported Outcomes	Quality Assessment (NOS)	Funding Source
Akins, 2000, US[27] Design: Single Retrospective Cohort	n = NR Age: 73 (11)y % Male: NR Race: NR Inclusion Criteria: Consecutive acute IS treated with IV TPA according to NINDS protocol treated by ER physician or neurologist Exclusion Criteria: NR	Use of ER protocols for management of acute stroke Note: Data is broken for two groups treated by ER physician (n=23) /or by neurologist (n=20)	Observational study examining ED physicians' ability to initiate thrombolysis	• Protocol deviation for ED physicians compared to neurologists • Number of pts treated by two tx groups	9/19	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated; TOAST = Trial of Org 10172 in Acute Stroke Treatment

Evidence Table 2 (cont'd): Single prospective cohort

Study Identification	Population Characteristics	Intervention	Technique /Dose /Timing	Reported Outcomes	Quality Assessment (NOS)	Funding Source
Hermier, 2003, France[28] Design: Single Prospective Cohort	n=28 Age: 65 (14)y % Male: 55.2 Race: NR Inclusion Criteria: Acute IS, with pre-tx & within 6 hr MRI; NIHSS >4 & no contraindication to tPA tx; with recanalization on MRI, or persistent occlusion on MRI Exclusion Criteria: Preexisting neurologic, psychiatric, or other illness confounding neurological evaluation; contraindications to MRI; movement artifacts precluding MRI interpretation; lacunar syndromes; presence of factors affecting time-to-peak analysis	Pre-treatment MRI scoring system for IS (recanalization n=18; persistent occlusion n=10)	CT + MRI (included three dimensional time of flight tube MRA; echoplanar imaging isotropic diffusion; and Perfusion MRI)	• NIHSS (60 d) • Relative & absolute time to peak/ 60 d lesion volume Note: Observational study correlating outcome with measured parameters	7/19	Délégation à la Recherche des Hospices Civilis de Lyon

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health

NOTE: Numerical values are mean (standard deviation) unless otherwise indicated; TOAST = Trial of Org 10172 in Acute Stroke Treatment

Evidence Table 2 (cont'd): Single prospective cohort

Study Identification	Population Characteristics	Intervention	Technique /Dose /Timing	Reported Outcomes	Quality Assessment (NOS)	Funding Source
Hill, 2000, Canada29 Design: Single Prospective Cohort	n=NR Age: mean 69.3y % Male: 55 Race: NR Inclusion Criteria: Acute IS, treated within 3 hr of symptom onset Exclusion Criteria: TIA (transient ischemic attack) or mild stroke; hx of subarachnoid hemorrhage; hypertension; hemorrhage, mass effect or edema, tumour or AVM on pre-tx CT; major surgery or trauma within 14 d; active internal bleeding; arterial puncture at a non-compressible site in the last 7 d; hx of hematological abnormality or coagulopathy or anticoagulation (PT > 15s, INR >1.4, PTT >4s, platelets <100,000/L)	Use of designated centers for acute stroke	Restructuring health care services, centralizing neurosurgical & neurological staff, using a modified model of NIHSS study with the aim of decrease time to tx	• Improvement in time intervals of onset to ER; onset to CT; ER to CT; ER to tx; CT to tx	5/19	Grants from HSF of Canada/ Alberta/ North West Territories; Medical Research Council of Canada & the Alberta Heritage Foundation for Medical Research Incentive Award

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated

Evidence Table 2 (cont'd): Single prospective cohorts

Study Identification	Population Characteristics	Intervention	Technique /Dose /Timing	Reported Outcomes	Quality Assessment (NOS)	Funding Source
Jahnke, 2003, US[30] Design: Single Retrospective Cohort	Age: NR % Male: NR Race: NR Inclusion Criteria: Acute stroke with mild to severe neurological deficits Exclusion Criteria: NR	Use of ER protocols for management of acute stroke Note: number of pts treated n=65	Observational study examining ED protocol	• Number of pts treated • Door-to-needle time decreased following implementation of the protocol	6/19	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated

Evidence Table 2 (cont'd): Single prospective cohort

Study Identification	Population Characteristics	Intervention	Technique /Dose /Timing	Reported Outcomes	Quality Assessment (NOS)	Funding Source
Kilpatrick, 2001, US[31] Design: Single Retrospective Cohort	n =51 Age: 61.7 (19-89)y % Male: 63 Race: NR Inclusion Criteria: Acute hemispheric IS within 24 hr post symptom onset, undergone CT, CT-Angiography & XeCT(xenon-enhanced-CT), CBF(cerebral blood flow); NIHSS score 1-26 Exclusion Criteria: posterior circulation symptoms	CT perfusion/ angiography for IS (n=51)	CT+ CT-Angiography + XeCT CBF/ within 24 hr post onset / completed at mean 44.5 min, range 15-223 min post onset	• Association of CBF, and infarction rates • Association of CT angiogram occlusion with infarction rate	5/19	Praxair

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated

Evidence Table 2 (cont'd): Single retrospective cohort

Study Identification	Population Characteristics	Intervention	Technique /Dose /Timing	Reported Outcomes	Quality Assessment (NOS)	Funding Source
Smith, 1999, US[33] Design: Single Prospective Cohort	n=37 (treated pts) Age: 63 (16)y, 22-87y % Male: 68 Race: White 86%; Black 11%; Asian 3% Inclusion Criteria: Acute IS treated with TPA, presented to ER 64 (29) min post onset Exclusion Criteria: NR	Use of ER protocols for management of acute stroke (n=37)	Observational study examining the ability of ED physicians to treat thrombolysis	• Onset-to-ED; onset-to needle time • Door to needle time (also: door-to physician; door-to-CT)	8/19	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated

Evidence Table 2 (cont'd): Case-control design

Study Identification	Population Characteristics	Intervention	Technique /Dose /Timing	Reported Outcomes	Quality Assessment (NOS)	Funding Source
Agarwal, 2004, US[34] Design: Case Control	n=83 Age: IG 70 (15)y; CG 71 (15)y % Male: IG 61; CG 47 Race: White IG 79%; CG 88% Inclusion Criteria: Acute IS (according to TOAST) <3 hr post symptom onset (IG) or 3-6 hr post onset & pts excluded for IV TPA based on NINDS criteria (CG) Exclusion Criteria: Cerebral hemorrhage/ NINDS criteria for thrombolytic tx	CT perfusion/ angiography for IS (n=66) C: Control (n=17)	I: CT/ 1.4 (0.7) hr & at 24 hr post onset + IV tPA/ 46-90 mg (0.9 mg/kg, max 90 mg)/ 2.3 (15) hr post onset C: CT/ 1.8 (1.1) hr & at 24 hr post onset + IA tPA/ 14-20 mg/ 4.4 (1.1) hr post onset	• Correlation with hyperdense middle cerebral artery signs (HCMAS) and outcomes • NIHSS (baseline, 24 hr post onset, discharge) • mRS (90 d)	8/19	NINDS grant

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health; TOAST = Trial of Org 10172 in Acute Stroke Treatment
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated

Pre-Post Studies

Evidence Table 3: Pre-post design

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes	Quality Assessment	Funding Source
Kay, 1993, Hong Kong[35] Design: Pre-Post	n=10 Age: 49-64y % Male: 50 Race: NR Inclusion Criteria: ICH confirmed by CT 8-48 hr pre-recruitment; systolic BP >180 mmHg, diastolic BP >100 mmHg Exclusion Criteria: NR	Antihypertensive therapy for ICH (n=10)	IV Ketanserin injection/ single does up to 10 mg/ 10-52 hrs post symptom onset	• Systolic arterial pressure (0-2 hr)* • Mean intracranial pressure • Cerebral perfusion pressure (0-2hr)*	NA	NR
Lattimore, 2003, US[32] Design: Pre-Post	n=327/511 pts admitted to the hospital met inclusion criteria for IS from Jan 2000 to Dec 2001 Age: 76 (range 27-95)y % Male: 51 Race: NR Inclusion Criteria: Acute IS < 6 hr (53% within 3 hr post onset), with persistent neurological deficits, & all inclusion criteria based on NINDS & guidelines from a Special Writing Group of the AHA Exclusion Criteria: Based on NINDS & guidelines from a Special Writing Group of the AHA	I: Use of designated centers for acute stroke	I: Around the clock coverage by stroke team	• Time to tx • Correlation of establishment of stroke center and number of pts treated with tPA	NA	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health
NOTE: Numerical values are mean (standard deviation) unless otherwise indicated
Quality of Pre-post studies was not determined.

Evidence Table 3 (cont'd): Pre-post design

Study Identification	Population Characteristics	Intervention (I) /Comparator (C)	Technique /Dose /Timing	Reported Outcomes	Quality Assessment	Funding Source
Nishiyama, 2000, Japan[36] Design: Pre-post	n=22 Age: 64 (±15, range 47-79) y % Male: 50 Race: NR Inclusion Criteria: Acute putaminal hemorrhage secondary to hypertension, with surgical drainage of hematoma Exclusion Criteria: history of liver or renal damage	I: Antihypertensive therapy for ICH (n=22)	I: Nicardipine infusion/ 484 ± 343 (138-826) mg for 213 ± 114 (92-323) hr	• BP*, HR, conscious level, Vmca, pulsatility index • Intracranial pressure • Cerebral perfusion pressure • Platelet counts • CT signs of change in bleeding and/or brain edema	NA	NR

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health

NOTE: Numerical values are mean (standard deviation) unless otherwise indicated; TOAST = Trial of Org 10172 in Acute Stroke Treatment

Quality of Pre-post studies was not determined.

Summary Table: Intervention J: Community education for stroke (excluded pre-post studies)

Study Identification	Setting	Population Characteristics	Intervention /Outcome	Limitations
Alberts,1992, US[37] Design: Pre-post	University Hospital (Duke/Durham)	Cerebral infarction; stroke-in-evolution; (ICH); subarachnoid hemorrhage Pre-educational: n=290 Post-educational: n=189	Community education program, professional education and helicopter transport/ Time delay in presentation & referral	Intervention mixed with other program changes; Lacks clinical outcomes; diagnoses differed pre and post
Barsan, 1994, US[38] Design: Pre-post	3 university & 9 community hospitals (including 2 teaching hospitals)	Pts within 24 hrs post onset (NIH tPA pilot study: Feb 1987-Aug 1989) ; n=1948	Community education program / Time of onset to hospital arrival	Retrospective evaluation of delay times coincident with program implementation; Unable to separate secular trends; Stroke severity was not accounted for at baseline
Becker, 2001, US[39] Design: Pre-post	King County (Washington) resident community	English speaking residents, randomly chosen & willing to participate in a telephone survey: n=1058	Community base education campaign/ Stroke knowledge (questionnaire based)	No measurement of clinical outcomes

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health

NOTE: Numerical values are mean (standard deviation) unless otherwise indicated; TOAST = Trial of Org 10172 in Acute Stroke Treatment

Quality of Pre-post studies was not determined.

Summary Table: Intervention J: Community education for stroke (excluded pre-post studies)

Study Identification	Setting	Population Characteristics	Intervention /Outcome	Limitations
Smith, 1999, US[40] Design: Pre-post	2 university hospitals	Paramedic Trainees: n=22 Stroke pts transferred by paramedics: n=84 (32 were transported by trained paramedics; 29/32 had stroke dx)	Educational program on stroke to improve paramedic accuracy in stroke recognition/ Paramedic test scores/ accuracy in identification of stroke victims	No measurement of clinical outcomes; Program directed at paramedics not general public
Weinhardt, 1999, US[41] Design: Pre-post	NR	Stroke patients: n=28	Education video to improve case management of stroke pts Pts knowledge of stroke (4 items from NIHSS)	No clinical outcomes

US = United States; NR = not reported; NA = not available; n = number of participants; pts = patients; y = year; mo = month; hr = hour; min = minutes; s = seconds; mg = milligrams; mL = millilitres; mmHg = millimetres of mercury; kg = kilogram; IU = international units; mmol/l = millimoles / litre; MHz = megahertz; IG = intervention group; CG = control group; BP = blood pressure; HR = heart rate; IS = ischemic stroke; ICH = intracranial hemorrhage; ER = emergency room; IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; tx = treatment; hx = history; IV = intravenous; IA = intra arterial; tPA = recombinant tissue plasminogen activator; S = significance; * = Significance (S) of statistical analysis; MCA = middle cerebral artery; AVM = arteriovenous malformation; Vmca = velocity in the middle cerebral artery; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health and Stroke Scale; ECASS = European Cooperative Acute Stroke Study; GCS = Glasgow Coma Scale; mRS = Modified Rankin Scale; GCS = Glasgow Coma Scale; NOS = Newcastle-Ottawa Scale; HSF = Heart and Stroke Foundation; AHA = American Heart Association; NHS = National Health Service; NIH = National Institutes of Health

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Quality of Pre-post studies could not be determined.

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