TITLE: Technologies Assisting in Remote Consultations for the Diagnosis of Stroke: A Review of the Clinical Evidence

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CONTEXT AND POLICY ISSUES

In Canada, strokes are responsible for approximately 16,000 deaths per year, making it the fourth highest cause of death.[1] For non-fatal cases, the burden associated with stroke is heavy for both patients and caregivers due to long-term disability, lowered ability to perform daily tasks, the cost of care, and lost productivity.[2] Strokes can be hemorrhagic or ischemic, with ischemic strokes accounting for approximately 80% of all strokes. In order to decrease the burden and increase positive outcomes for patients with acute stroke, rapid assessment and treatment is important.[2,3]

One treatment option for acute ischemic stroke is systemic thrombolysis treatment, using tissue plasminogen activator (tPA). Thrombolysis treatment dissolves the clot that is obstructing blood flow to the brain, preventing permanent damage and is therefore associated with favourable outcomes.[2,3] There is a narrow treatment window for thrombolysis treatment; it must be delivered within three hours of symptom onset, and it requires specific neurological expertise in order to guide the decision-making regarding ideal candidates for the treatment. As most stroke experts are located in major centres, patients in rural or remote areas are unlikely to receive thrombolysis treatment unless remote physicians are able to liaise with stroke experts in order to help guide decision-making and treatment planning. Telehealth and telemedicine are options used in order to link remote physicians with experts for this purpose.[2,3]

Telehealth and telemedicine can include telephone consultation, the transfer of digital imaging results via email or secure website, videoconferencing where the clinical encounter is guided by a stroke expert in a stroke centre, and various combinations of these modalities. This report will review the clinical evidence available regarding technologies used that assist with remote consultations for the diagnosis and treatment planning for patients presenting with symptoms of acute stroke or transient ischemic attack.

RESEARCH QUESTION

What is the clinical evidence regarding technologies used for remote consultations with neurology specialists in order to optimally diagnose and administer initial treatment for patients presenting with suspected acute stroke or transient ischemic attack?

KEY FINDINGS

For the diagnosis and treatment of ischemic stroke, it is likely that telemedicine is a legitimate option to guide treatment decisions, including the administration of tPA, at rural and remote hospitals and results in positive outcomes without compromising patient safety. Telemedicine technologies that allow for image transfer tend to perform better than technologies that do not. The majority of the data included in this review is based on non-randomized patients and non-blinded assessors and thus should be interpreted with caution.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and October 24, 2013.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of relevant titles or abstracts were retrieved, and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with acute stroke symptoms or symptoms of transient ischemic attack symptoms that require a consultation with a neurologist but presenting to health care settings without a neurology expert.
Intervention	Technologies remotely linking experts in tertiary areas with rural/remote patients
Comparator	Any/None
Outcomes	Timely diagnosis, timely access to treatment, safety, quality of diagnosis, reliability of diagnosis, optimal utilization of appropriate treatment
Study Designs	HTA, SR, MA, RCT, NRS

HTA = health technology assessment; MA = meta-analysis; NRS = non-randomized studies; RCT = randomized controlled trials; SR = systematic review

Exclusion Criteria

Studies were excluded if they did not fit the selection criteria, were duplicate publications, were published prior to 2008, or were examined in an included systematic review. Studies in the pre-hospital setting and studies for which the outcome was determination of stroke severity or time-to-treatment but did not include patient outcomes were also excluded.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was based on study design.

The methodological quality of the included systematic reviews and meta-analyses was evaluated using the "assessment of multiple systematic reviews" (AMSTAR).[4] AMSTAR is an 11-item checklist that has been developed to ensure reliability and construct validity of systematic reviews. The quality of RCTs and NRS was assessed using the Downs and Black checklist.[5] A numeric score was not calculated for each study. Instead, strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 316 citations were identified in the literature search, 277 of which were excluded based on title and abstract screening due to their irrelevance to the research questions. The full text documents of the remaining 39 articles were retrieved and one additional article was identified from the grey literature search. Of the 40 articles examined in full text, 23 did not meet the inclusion criteria and were excluded, leaving 17 included articles reporting on one HTA,[3] one systematic review,[2] one RCT,[6] and 14 non-randomized studies.[7-20]

A PRISMA diagram illustrating the study selection process is presented in Appendix 1. Studies that reported on distance stroke consultation, but did not report patient outcomes and therefore may be of interest, as well as studies examining the implementation or barriers to implementation and uptake of telemedicine programs, are provided in Appendix 2.

Summary of Study Characteristics

Study Design

One HTA,[3] one systematic review,[2] one RCT,[6] and 14 non-randomized studies[7-20] met the inclusion criteria and were included in the review. The non-randomized study types included three before-and-after studies,[7,10,19] three prospective cohort studies,[9,13,14] three retrospective cohort studies,[15-17] two retrospective controlled studies,[12,20] and one each of retrospective controlled follow-up,[18] retrospective case series,[11] and prospective case series.[8]

Population

The included randomized and non-randomized studies were conducted in the USA,[6-9,14,17,20] Australia,[10] the UK,[11] Austria,[12] Finland,[13] Canada,[15] Thailand,[16] Germany,[18] and Spain.[19] The

identified systematic review[2] and HTA[3] included studies from Canada, China, Finland, Germany, and the United States.

Overall, the baseline characteristics of the included patients were generally comparable. All studies included patients presenting to emergency departments or stroke centres with symptoms of acute stroke or TIA. Of the studies that reported the mean age of patients, one[20] study examined patients with a mean age younger than 65, 10[2,6-9,12,14,15,17,19] between 65 and 75, one[10] older than 75, and no studies had a mean age older than 80. One[17] study reported a significant difference in age between the intervention groups (P = 0.05 between telemedicine and patients treated at a stroke centre). Most studies reported no significant differences between the number of male and female subjects, with the exception of one NRS[10] that included a population that was 69% female (P = 0.02 vs. males). Of the studies that reported comorbidities such as diabetes, hypertension, hyperlipidemia, and previous stroke or TIA, while there was the occasional imbalance within the studies, the percentage of patients with the various comorbidities between the studies was generally comparable.

The number of patients included in the randomized and non-randomized studies ranged from 44 patients[15] to 3,060 patients.[18] The HTA[3] included 14 studies reporting on 10,598 patients, with the number of patients examined in the included studies varying from 14 to 4,727. The systematic review[2] included 18 studies but did not report the overall number of patients analyzed.

Interventions and comparators

In most of the studies, telemedicine (TM) was defined as two-way videoconferencing or a combination of telephone and image transfer, in which physicians in the rural or remote areas – "spoke" physicians – communicated with experts at the stroke centre – "hub" physicians – and were guided through the clinical consultation and the treatment decision-making with the help of the hub physicians. The hub physicians also had access to laboratory and imaging results either orally (for laboratory results) or electronically (either by transfer of images on a secure website, digital imaging and communications in medicine viewers, or occasionally, email transfer). Telephone communication-only (TC or TC-only) was defined as the use of oral communication only for the consultation between spoke and hub physicians – laboratory results were communicated orally, but imaging results were not able to be viewed by hub physicians.

Many comparisons were identified:

- Four[2,3,6,15] studies included a comparison between telemedicine and telephone consultation.
- Six[2,12-14,17,20] studies included a comparison between patients treated remotely by telemedicine or telephone compared with those treated at a stroke centre.
- Three[7,10,19] studies compared the outcomes of patients who were treated before the introduction of telemedicine with those who were treated after.
- One[3] study included outcomes for telephone consultation with image transfer versus without.
- One study[11] compared those who received treatment from a local stroke physician versus those who were treated via telephone consultation when the local physician was not present.

- One[8] study compared the outcomes of patients who were treated via telephone consultation versus no telephone consultation.
- One[18] study compared the outcomes of patients who were treated with any type of treatment via telemedicine consultation versus no TM consultation.
- One[13] study compared the outcomes of patients who received tPA administration after telemedicine consultation versus those who did not
- One study[9] compared the outcomes of patients who did not receive tPA treatment, received tPA treatment, tPA treatment plus intra-arterial (IA) therapy, and IA therapy alone, all guided by telemedicine.
- Three[2,3,16] studies included information for telemedicine or video consultation without a comparison.

Outcomes

The main outcomes of interest included both shorter and longer-term outcomes. The short-term outcomes reported were:

- Correct decision-making regarding treatment administration: two studies[2,7]
- Diagnostic accuracy: three studies[2,3,6]
- Thrombolytic use or change in thrombolytic use: seven studies[2,3,6,7,10,16,19]
- Technical difficulties with the communication medium: two studies[6,10]
- Time to treatment: 16 studies[2,3,6-17,19,20]
- Functional outcomes (at discharge or after 7 days): seven studies[7,9,11,12,17,19,20]
- Mortality (in-hospital or within 7 days): eight studies[2,7,9,12,13,15,17,20]
- Symptomatic and asymptomatic ICH (in-hospital, within 36 hours): three studies[8,12,17]

Longer-term outcomes reported were:

- Functional outcomes after 90-days: eight studies[6,10-16]
- Functional outcomes after 12 and 30 months: one study[18]
- Mortality (30 days and beyond): eight studies[3,11-16,18]
- ICH (symptomatic and asymptomatic: one study[14]

Total mortality and intracerebral hemorrhage where the timing was not specified was reported in four[2,6,8,10] and six[7,9,11,13,16,20] studies respectively.

The systematic review[2] and the HTA[3] included outcomes of patient and physician satisfaction with telemedicine.

Further detail regarding the study characteristics is presented in Appendix 2.

Summary of Critical Appraisal

The included HTA[3] was of high quality. A protocol was published *a priori*; a list of included and excluded studies was provided; important study and patient characteristics were described; the literature search included multiple databases and a hand search; there was duplicate study screening, data extraction, and critical appraisal; and the methods used to combine studies was appropriate – due to heterogeneity a narrative summary was presented. The only minor limitation was that publication bias was not assessed numerically; however the fact that unpublished studies were not included was mentioned as a limitation.

The included systematic review[2] had some major strengths as well as some major limitations. The major strengths were a comprehensive literature search including multiple databases and a hand search, duplicate selection and data extraction, and methods used to combine the findings of studies appropriate – due to heterogeneity, the authors elected not to pool studies, and a narrative review was presented. The major limitations included a lack of clarity regarding critical appraisal, lack of inclusion of lists of included and excluded studies, the lack of consideration regarding publication bias, and the lack of a conflict of interest statement. The lack of clarity regarding critical appraisal is especially problematic as it is possible that major conclusions were drawn based on studies that were not of high rigour or quality.

The included randomized trial[6] had more major strengths than limitations. Major strengths included that interventions, outcomes, patient characteristics, and findings were clearly reported, the included subjects and hospitals where the patients were treated were likely representative, patients were randomized, and those who assessed patient outcomes were blinded to the intervention. Main limitations were that patients were not blinded to the intervention and that it wasn't clear if the study was powered to detect a clinically important effect.

Many of the NRS had similar strengths. The objectives, interventions, and main outcomes were clearly described in all of the non-randomized studies.[7-20] The study subjects were likely representative of the overall population in all but four[10,16,19,20] of the included NRS. There were significantly more female than male patients in one NRS (P = 0.02),[10] the patients in each group were recruited from different environments (one rural, one urban) in one study,[12] the subjects in each group were recruited over different time periods in one study,[13] and one study reported little detail regarding patient characteristics and it was therefore unclear if the patients in the sample were representative of the overall population.[16]

Many of the non-randomized studies also had similar limitations. None of the studies randomized or blinded patients to the intervention[7-20] and the majority either did not blind assessors or it was unclear if assessors were blind to the intervention.[7,9,10,12-17,19,20] Thus, there may be an overestimation of the effects of the intervention. It was unclear if the study had sufficient power to detect a clinically important effect in 11 of the 14 non-randomized studies.[7,8,10-16,19,20] Eleven[7-10,12,14,16-20] of the 14 studies also did not clearly report the characteristics of the patients lost to follow-up, meaning that it is possible that patients that were not analyzed differ from those who remained in the study – which may change the result observed. Furthermore, three of the included studies[2,3,16] did not include comparative information and thus it is difficult to determine the effect sizes of the intervention in those studies.

Further detail regarding the critical appraisal is tabulated in Appendix 4.

Summary of Findings

Time to Treatment

<u>Telemedicine vs. Telephone Consultation</u>

Telemedicine was generally defined as audio and video contact between the spoke and hub physicians, patients and included the remote viewing of images. Telephone consultation involved communication by telephone-only, without the remote viewing of images.

The included randomized trial[6] resulted in no significant differences in time (reported in minutes, mean ± standard deviation [SD]) between symptom onset to a treatment decision (TM 188.2 ± 138.2 vs. TC 164.8 ± 28.6; P = 0.067), symptom onset to tPA treatment (TM 164.6 ± 31.7 vs. TC 170.5 ± 17.2 P = 0.798), or patient arrival at the emergency department (ED) to a treatment decision (TM 100.5 ± 28.4 vs. TC 90.7 ± 27.9; P = 0.115)

In the Canadian retrospective cohort study,[15] no significant differences were found in the time elapsed between arrival at the ED and tPA treatment (P = 0.46) or between symptom onset and tPA treatment (P = 0.76) in TM versus TC treated patients.

Pre- vs. Post-Telemedicine implementation

No significant differences were found in the time elapsed (in minutes, mean ± SD) from symptom onset to treatment (pre-TM 129.8 ± 34 vs. post-TM 124.4 ± 34; P = 0.49) or from the arrival at the ED to treatment (pre-TM 74.2 ± 32.1 vs. post-TM 74 ± 29.1; P = 0.98) in one NRS.[7] In another NRS comparing the time elapsed from symptom onset to treatment, patients treated after the introduction of the TM program were treated significantly faster (pre-TM 210, SD 43 vs. post-TM 162, SD 84; P = 0.05).[19]

In the Australian study,[10] the time between symptom onset or arrival at the ED and treatment was not reported, but the time between arrival at the ED and when patients received CT imaging was not significant between the two groups (post-TM 70 min vs. pre-TM 80 min; P = 0.66).

Telemedicine vs Stroke Centre Treatment

In one included retrospective controlled study[12] there was no significant difference in the time elapsed (in minutes, mean ± SD) between symptom onset and tPA treatment between patients who were treated via telemedicine compared with those who were treated at a stroke centre (TM 113, SD 40 vs. SC 122, SD 47; P = 0.26). The time to tPA treatment was similar in a prospective cohort study[13] where time to tPA treatment (120 minutes) was reported only for the TM group.

In one included prospective cohort study,[14] no significant differences were found in the time between symptom onset to tPA treatment in the TM group versus SC-treated patients (TM 145.5, SD 42.8 vs. SC 156.7, SD 31.6; P = 0.09), but there was a significantly longer time between arrival to the ED and tPA treatment in the TM group versus those who were treated at the stroke centre (TM 89.9, SD 36.3 vs. SC 67.8, SD 26.1; P < 0.01). In the NRS reporting median time elapsed between symptom onset and tPA treatment,[17] time elapsed for patients receiving TM-guided treatment was lower than for those treated at the stroke centre, but the difference was not significant (P = 0.06).

One retrospective cohort study reported the time elapsed between the onset of symptoms to any type of treatment[20] and although the time to treatment was lower in TM-treated patients compared with those treated in an academic ED, this difference was not statistically significant (P = 0.0651). In this study, 50% of TM-treated and 35% of ED treated patients were treated within two hours of symptom onset.

Telemedicine

Telemedicine was generally defined as audio and video contact between the spoke and hub physicians, patients and included the remote viewing of images.

The HTA[3] reported four studies that measured the time elapsed between ED arrival and tPA administration (range 62.9 to 106 minutes) and one study that measured the time elapsed between symptom onset and any treatment (23% treated within 90 min, 60% within 120 min). Comparisons were not reported.

The included SR found that the mean time elapsed from symptom onset to tPA treatment ranged from 122 to 135.5 minutes and time elapsed from arrival to the ED to tPA administration ranged from 68 to106 minutes in video telemedicine studies.[2]

In the included retrospective cohort study[9] that compared the outcomes of patients who did not receive tPA treatment, received tPA treatment, tPA treatment plus intra-arterial (IA) therapy, and IA therapy alone, all guided by telemedicine, the amount of time elapsed between symptom onset to the administration of tPA was similar in patients who received tPA alone and those who received a combination of tPA and IA treatment (tPA 152 vs. tPA + IA 147; P = NR).

In one of the retrospective cohort studies reporting the time to tPA treatment in patients treated via telemedicine,[16] the time elapsed between symptom onset and tPA treatment was 160 minutes, and between arrival at the ED and tPA treatment was 54 minutes. No comparison was presented.

Telephone Consultation vs. No Telephone Consultation

In the included prospective case series that compared TC with no-TC[8] resulted in the same median time elapsed between the time patients arrived in the ED and the time treatment was initiated.

Telephone Consultation vs. Local Stroke Physician

In the retrospective case series[11] that compared outcomes for patients who received treatment from a local stroke physician versus those who were treated via telephone consultation when the local physician was not present, all patients received tPA treatment and the median time between arrival at the ED and the time tPA treatment was initiated was lower in the LSP group, however the significance was not reported.

Telephone Consultation

The included SR found that the mean time elapsed from symptom onset to tPA treatment ranged from 119 to 165 minutes in telephone consultation studies and time elapsed from arrival to the ED to tPA administration was reported as 105 in a single telephone consultation study.[2]

Use or Change in Thrombolytic Use

Telemedicine vs. Telephone Consultation

The rate of administration of tPA was the same (30%) in both the telemedicine and the telephone groups in the included randomized trial.[6] There were no differences in thrombolysis-related mortality.

Pre- vs. Post-Telemedicine Implementation

In one NRS,[7] there was a significant increase in the administration of tPA after the introduction of telemedicine (pre-TM 2.8% vs. post-TM 6.8%; P < 0.001). One adverse event deemed potentially tPA-related occurred. In a second NRS, the introduction of telemedicine resulted in more patients receiving tPA treatment, however the difference was not statistically significant (pre-TM 4.5% vs. post-TM: 9.6%; P = 0.07), nor was the difference between the number of patients who experienced clinical benefit from thrombolysis treatment (pre-TM 70% vs. post-TM 59%; P = 0.39).[19]

In the Australian NRS,[10] thrombolysis use increased with the availability of telemedicine: 33% of eligible patients received thrombolysis therapy when TM was available, compared to no patients when TM was not available. This amounted to 6.2% of all acute stroke patients receiving thrombolysis therapy in the first year that telemedicine was introduced and there were no cases of intracerebral hemorrhage or deaths that were directly linked to tPA therapy.

The included HTA found that tPA increased following the introduction of TM in three studies: from 0 cases to 86 in one study, from 0.8% to 4.3% (P < 0.001) in one study, and from 0% to 5.6% (P value not presented) in one study.[3] It also found a 72% increase in tPA use following the introduction of telephone consultation in one study. It was unclear if there were any tPA-related adverse events that would indicate inappropriate use.

Correct Decision Making

Telemedicine vs. Telephone Consultation

In the included SR, one study reported on correct decision making regarding treatment administration.[2] Correct decision making occurred 98% of the time for TM, 82% for telephone consultation (Odds Ratio [OR] 10.9, 95% confidence interval [CI], 2.7 to 44.6; P = 0.0009). The definition of correct decision making was not presented.

Correct treatment decision making, as judged by blinded assessors, was reported in 85% of patients in the telemedicine group and 89% in the telephone group in the included randomized trial; the different was not significant (P > 0.999).[6]

Pre- vs. Post-Telemedicine Implementation

Incorrect decision-making, as judged by blinded assessors in an American non-randomized before and after study[7] was reported as occurring 0.2% of the time in the pre-telemedicine group and 0.3% in the post-TM group (P = 0.7).

Diagnostic Accuracy

The included HTA included one study that reported significant differences between the diagnostic accuracy in patients diagnosed via TC-only, TC with image transfer, and TM using videoconferencing.[3] TC with image transfer and TM using videoconferencing both resulted in significantly better diagnostic accuracy when compared with TC-only consultation (P<0.0005). No gold standard or definition of diagnostic accuracy was reported.

The included SR also found a significant difference in diagnostic accuracy. One study was included and diagnostic accuracy was 87.7% for TM versus 63.8 % in the telephone group (P =0.001).[2] No gold standard or definition of diagnostic accuracy was reported.

Functional Outcomes

Functional outcomes considered to be "good" on the Modified Rankin Scale (mRS) were generally defined to be a score of zero or one, which indicates little to no disability, and defined to be a score between 95 and 100 on the Barthel Index.

Telemedicine vs Telephone Consultation

The included randomized study[6] found no difference between good 90-day functional outcomes on the Barthel Index (59% of telemedicine patients and 58% of telephone patients had a score of 95 to 100; P = 0.77) or the mRS (46% of telemedicine and 48% of telephone patients had a score of 0 to 1; P = 0.61)

In the Canadian retrospective cohort study,[15] there were no significant differences in 90-day functional outcomes between TM and TC patients (P = 0.689).

Telemedicine vs Stroke Centre Treatment

In one included retrospective controlled study[12], there was no significant difference in good 90-day functional outcomes on the mRS (47% of TM patients and 43% of SC patients had a score of 0 to 1; P = 0.69). Good functional outcomes on the mRS (34.8% of patients had a score of 0 to 1) were reported for the overall population of one included NRS,[17] however the time period was not reported.

In two included prospective cohort studies[13,14], the percentage of patients with good 90-day functional outcomes on the mRS was not significantly different for patients who received TM-guided tPA therapy than those who received tPA therapy at a stroke centre (P = 0.289,[13] P = 0.09[14]).

Telemedicine vs. No-Telemedicine

The included HTA included one study that reported a significant difference between TM and no-TM with respect to "poor outcomes" after 90 days (P < 0.025) and that TM independently reduced the probability of a poor outcome (OR 0.62, 95% CI 0.52 to 0.74; P < 0.0001).[3]

Telemedicine

In one retrospective cohort study,[16] the percentage of patients who received TM-guided tPA treatment with a good 90-day functional outcome, as measured on the mRS, was 42%. No comparison was reported.

Telephone Consultation vs. Local Stroke Physician

In the retrospective case series[11] that compared outcomes for patients who received treatment from a local stroke physician versus those who were treated via telephone consultation when the local physician was not present, good outcomes on the mRS after 90 days were similar in the two groups (LSP 36% vs. TC 31%) as were mRS scores indicating moderate to severe disability (LSP 17% vs. TC 20%). Statistical significance was not reported.

Mortality

Telemedicine vs. Telephone Consultation

The included HTA included one RCT that reported six-month mortality outcomes. TM-treated patients had significantly lower mortality than TC patients ($P < 0.025$).[3]
Overall mortality in the randomized study[6] was 11% in the telemedicine group and 4% in the telephone group (P = NS) and for patients receiving tPA treatment (n = 8 in each group), 1 patient in the telephone group died and no patients in the telemedicine group died. The timing of the deaths was not reported.

Overall 7-day and 90-day mortality were 9% and 22.5%, respectively, in the Canadian retrospective cohort study,[15] though the information was not reported for the different groups.

Pre- vs. Post-Telemedicine Implementation

There was no statistically significant difference in in-hospital mortality before or after the introduction of telemedicine (pre-TM 7.4% vs. post-TM 10.9%; P = 0.59) in 16195

In the Australian before and after study,[10] there was no difference in mortality rates after the introduction of telemedicine between patients for whom TM was used (13%) versus those not used (10%) (P = 0.6).

Telemedicine vs Stroke Centre Treatment

In one included retrospective controlled,[12] in-hospital mortality was lower in TM patients than in SC-treated patients, but this was not significant (P = 0.056) and the difference in 90-day mortality between TM patients and SC-treated patients was also not statistically significant (P = 0.248). The difference in in-hospital mortality was also insignificant in another included NRS (P = 0.57).[17]

In two included prospective cohort studies,[13,14] 90-day mortality for patients who received tPA treatment was not significantly different between patients treated via TM than in SC-treated patients (P = 0.662,[13] P = 0.6[14]).

90-day mortality for TM treated patients in one non-randomized retrospective study was 6%, however no comparison was reported.[20]

Telemedicine vs. No Telemedicine

The retrospective controlled follow-up comparing patients who received TM compared with those who did not[18] reported no statistically significant differences in 90-day (adjusted OR 0.93, 95% CI 0.74 to 1.17), 12 month (adjusted OR 0.98; 95% CI 0.80 to 1.19), and 30 month (adjusted OR 0.95, 95% CI 0.79 to 1.14) mortality.

Telemedicine

In the included prospective cohort study[9] that compared the outcomes of patients who did not receive tPA treatment, received tPA treatment, tPA treatment plus intra-arterial (IA) therapy, and IA therapy alone, all guided by telemedicine, mortality at discharge was 2.7% in patients who did not receive tPA, 5.4% in those who received tPA and 13.3% in patients who received tPA and intra-arterial therapy. It was unclear if these differences were statistically significant (P = NR)

In one retrospective cohort study reporting 90-day mortality for patients who received TM-guided tPA treatment, mortality was 14% and a comparison was not reported.[16]

Overall mortality rates for patients who received TM-guided tPA treatment reported in the SR ranged from 0% to 50% (the 50% represented one of two patients treated with tPA).[2] Two of the included studies in the SR reported in-hospital mortality for patients who received TM-guided tPA treatment as 3.5% and 10.4%.

Telephone Consultation vs. No Telephone Consultation

In the included prospective case series that compared TC with no-TC,[8] mortality rates were lower in the TC group (5.6%) than in the no-TC group (13.2%), however it was unclear if this was statistically significant (P = NR).

Telephone Consultation vs. Local Stroke Physician

Ninety-day mortality was similar between those who were treated by a local stroke physician (18.1%) and through telephone consultation with an expert (19.6%) in the retrospective case series. The statistical significance of the difference was not reported.[11]

Telephone Consultation

Overall mortality rates of for patients who received TC-guided tPA treatment reported in the SR ranged from 0% to 39%.[2]

Intracerebral Hemorrhage (ICH)

Pre- vs. Post-Telemedicine Implementation

In one NRS,[7] though the occurrence was lower, statistically significant differences in symptomatic ICH were not reported after the introduction of telemedicine (pre-TM 3.7% vs. post-TM 0.9%; P = 0.34).

Telemedicine vs Stroke Centre Treatment

In one included prospective cohort study,[13] ICH rates were lower in patients treated with tPA via TM (6.7%) than in those receiving tPA at a stroke centre (9.4%), however statistical significance was not reported. In a second NRS comparing tPA treatment administered via TM versus SC, there were no statistically significant differences between rates of symptomatic (P = 0.1) or asymptomatic ICH (P = 0.7)

In the retrospective cohort study reporting rates of symptomatic ICH <36 hours after tPA treatment, there were no statistically significant differences between patients who received TM-guided care compared with those who received stroke-centre guided care.[17] In the retrospective controlled study that reported rates of symptomatic ICH but did not report the time elapsed, there was no statistically significant difference between TM and academic ED treated patients (P = 1.0).[20]

Telemedicine

In the included prospective cohort study[9] that compared the outcomes of patients who did not receive tPA treatment, received tPA treatment, tPA treatment plus intra-arterial (IA) therapy, and IA therapy alone, all guided by telemedicine the rates of symptomatic ICH were statistically significantly different in patients who did not receive tPA (0%) than in those who received tPA treatment(1.6%) (P ≤ 0.01).

In one retrospective cohort study,[16] 2% and 13% of patients treated with TM-guided tPA had symptomatic and asymptomatic ICH, respectively. The timing of ICH and a comparison with another intervention were not reported.

Telephone Consultation vs. Local Stroke Physician

In the retrospective case series[11] that compared outcomes for patients who received treatment from a local stroke physician versus those who were treated via telephone consultation when the local physician was not present, ICH was more common in patients treated by local stroke physicians (14.3%) than those who were treated via telephone consultation (7.4%), however statistical significance was not reported.

Technical Difficulties

The randomized study[6] reporting technical difficulties as an outcome reported technical problems in 74% of telemedicine consultations and none of the telephone consultations. No technical problems influenced the outcome of the treatment decision, however, some did influence the amount of time the consultation took.

In the prospective cohort study[14] that compared outcomes before and after the introduction of telemedicine, technological difficulties occurred in 25% of consultations.

Further detail regarding study outcomes are included in Appendix 5.

Limitations

With respect to the included literature, one of the limitations is the change in technology through the years. The HTA included in this review examined literation from 2000 to 2006. Screen resolution, internet bandwidth, and videoconferencing have improved substantially since 2000, as well as since the oldest included primary study, published in 2008. It is possible that the results of studies using older technologies are not generalizable to the current setting.

Another limitation is the lack of data based on randomized patients. Although the majority of the studies were comparative, the lack of randomization may have introduced bias and there may be differences between the intervention groups that were not known or not accounted for in the analyses. Furthermore, none of the studies included patient blinding and a minority blinded outcome assessors to the type of consultation the patients received. This could have influenced reporting of positive outcomes associated with telemedicine.

The lack of Canadian data may limit the generalizability of the results to the Canadian population. One included study was performed on Canadian patients and the included systematic review and HTA also contained few Canadian studies. However, since the telecommunication technologies in Canada and the United States are quite similar, it is likely that the success of the remote technologies is transferrable to Canadian settings, and many of the included studies were conducted in the United States.

Although most of the studies using telemedicine or telephone consultation took place in hospitals that were not tertiary centres with stroke experts or stroke centres, these were not always remote hospitals. Many, especially in the case of the American studies, were close to urban centres and likely had high quality internet and phone connections. Thus results may not be generalizable to remote locations with lower quality connections. Patient volume and clinician expertise also varied in the studies, which may limit generalizability to settings where there is particularly low volume of patients and limited experience with patients presenting with stroke symptoms.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This report aimed to evaluate the clinical evidence available regarding technologies used that assist with remote consultations for the diagnosis and treatment planning for patients presenting with symptoms of acute stroke or transient ischemic attack.

One HTA, one systematic review, one RCT, and 14 non-randomized studies comparing various distance-consultation methods and reporting on various outcomes were identified and the results were somewhat mixed. Generally, there was an increase in tPA use following the introduction of telemecidine programs – whether they were with or without video or image transfer. In general, telemedicine programs that included videoconferencing and/or technologies that allowed the transfer diagnostic imaging results performed better than telephone consultation alone, though the differences were not always statistically significant. Diagnostic

accuracy was the only outcome for which the included studies all found that telemedicine technologies with image transfer had significantly better diagnostic accuracy than those without.

In studies comparing outcomes in patients treated in centres before and after the introduction of a telemedicine program, although outcomes such as time to treatment and use of tPA treatment was often better after the introduction of a telemedicine program, these differences were rarely statistically significant. Similar long-term functional outcomes were found in patients receiving treatment guided by telephone consultation versus telemedicine and by telemedicine versus at a stroke centre, and generally better long-term functional outcomes were found in patients who received telemedicine-guided treatment versus those who did not (and who did not have access to a stroke expert).

Generally, differences in important outcomes such as time to treatment, mortality, and functional outcomes were not significantly different in patients treated by physicians who were using telemedicine or telephone consultation in order to diagnose and treat patients (including tPA therapy) than in patients who were being treated by physicians at an academic stroke centre. Thus, it is likely that telemedicine is a legitimate treatment option that can be used at rural and remote hospitals without compromising patient safety. Telemedicine technologies that allow for image transfer tend to perform better than technologies that do not. The majority of the data included in this review is based on non-randomized patients and non-blinded assessors and thus should be interpreted with caution.

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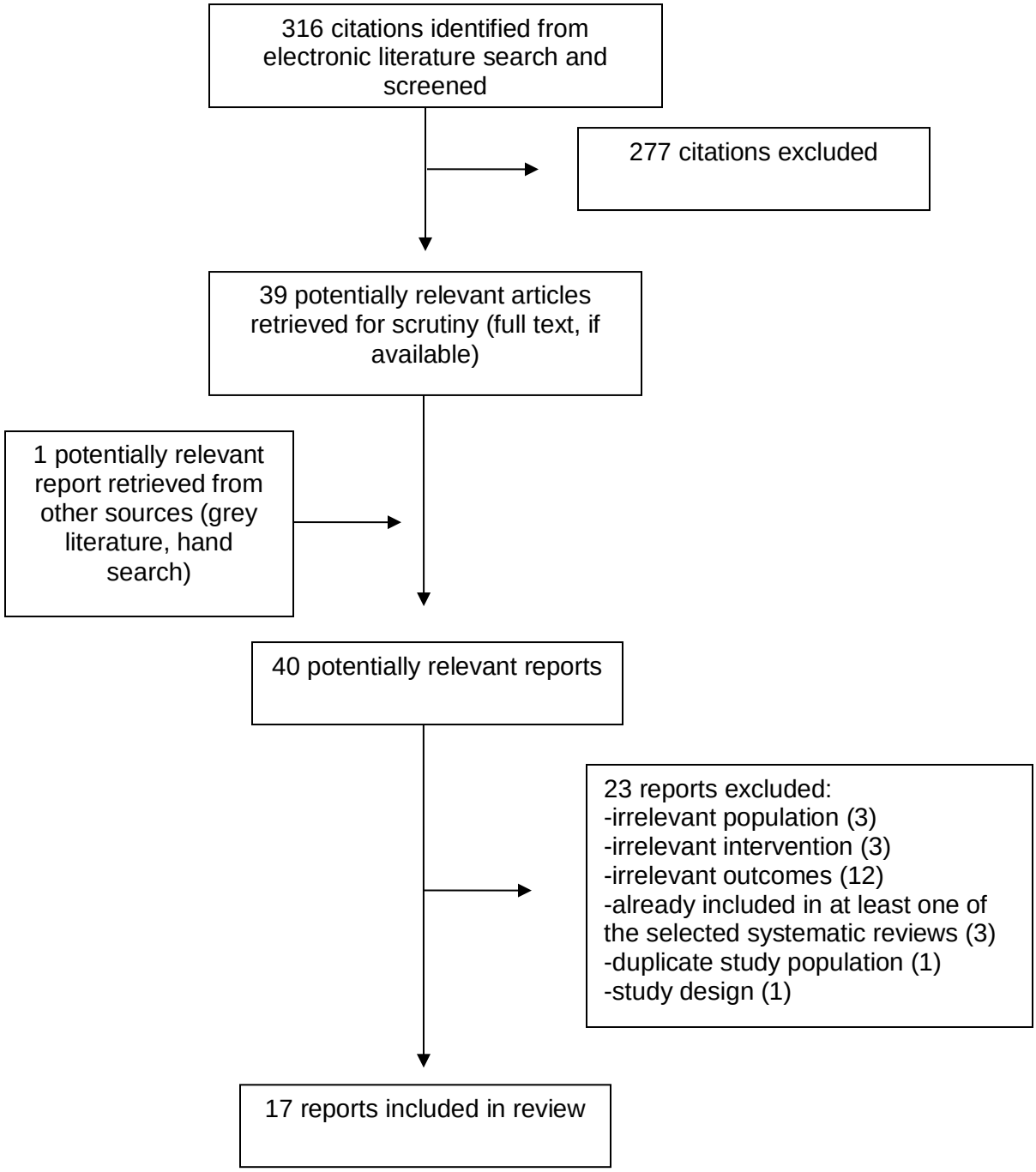
22. Supplementary table 1: general characteristics of studies meeting the inclusion criteria. Supplementary material for: Johansson T, Wild C. Telemedicine in acute stroke management: systematic review. Int J Technol Assess Health Care. 2010 Apr;26(2):149-55.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional Information of Potential Interest

Clinical Studies that Did not Examine Patient Outcomes

Randomized Controlled Trials

1. Demaerschalk BM, Bobrow BJ, Raman R, Ernstrom K, Hoxworth JM, Patel AC, et al. CT interpretation in a telestroke network: agreement among a spoke radiologist, hub vascular neurologist, and hub neuroradiologist. Stroke. 2012 Nov;43(11):3095-7.

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Non-Randomized Studies

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Studies Describing Implementation or Examining Barriers to Implementation and Uptake

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APPENDIX 3: Characteristics of Included Studies

Table 2: Characteristics of the Included HTA and SR			
Types of Studies Included, Study Objective	**Patient Populations**	**Type of Distance Stroke/Telemedicine Program**	**Main Outcomes**
Johansson & Wild, 2010[2]			
RCTs (2 studies), CCTs (1 study), and observational designs (15 studies) including case series and prospective cohorts. Dates of included studies ranged from 2003 to 2008. To assess the feasibility, acceptability, and reliability for treatment delivery of telemedicine systems for the management of acute stroke.	Patients with suspected acute stroke in Canadian (1), Chinese (1), German (3), and American (10) centres. Total number of patients included not reported. Mean age: 66.2 Females: 45%	Real-time two way video conferencing (10 studies) Telephone consultation vs video consultation (3 studies) Telephone consultation (5 studies)	Feasibility and acceptability of the program, time to consultation, time to treatment, successful treatment, death, disability, tPA administration
Deshpande et al., 2008[3]			
RCT (1), CCT (1), prospective and retrospective CS (12). Dates of included studies ranged from 2000 to 2006. To assess the health outcomes of telestroke both for acute care and rehabilitation.[a]	Patients with suspected acute stroke presenting to acute care settings in Canada (2), China (1), Finland (1), Germany (4) and the USA (6). N = 10,598 (range 14 to 4,727)	Majority of studies (11) examined videoconference telemedicine programs with 2-way communication and transfers of imaging results. One study examined teleradiology, 2 studies examined telephone consultation.	Mortality, time to treatment, functional outcomes, correct diagnosis.

CCT = controlled clinical trial; CS = case series; RCT = randomized controlled trial; tPA = tissue plasminogen activator; USA = United States of America
[a]results for acute-care only presented in this review

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
Randomized Controlled Trials			
Demaerschalk et al., 2010[b] Single academic hub with 2 remote "spoke" sites (299 to 330 kilometers from the hub) in the USA. To determine the feasibility of establishing a single-hub, multi-rural spoke hospital telestroke research network across a large geographical area using the STRokE DOC protocol. RCT	54 patients (27 randomized to TM; 26 randomized to TC) Mean age: TM: 66.4 ± 13.6 TC: 66.1 ± 13.6 Female: TM: 48% TC: 52% Coronary disease: TM: 41% TC: 19% Diabetes: TM: 23% TC: 30% Hyperlipidemia: TM: 37% TC: 33% Hypertension: TM: 82% TC: 67% Known family history of stroke/TIA: TM: 15% TC: 7%	Telemedicine: audio and video contact between the spoke and hub physicians, patients (and those who accompanied patients to the hospital). NIHSS performed in conjunction with the spoke physicians, test results communicated orally, by fax, or DICOM viewer for CT images. Telephone only: hub physician communicated with the spoke sites by telephone only. Consultations were conducted by phone, no images were seen by the hub physicians.	Thrombolytic use, 90 day functional outcomes, rates of ICH, technical difficulties, time to treatment

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
	Patients had to present within 3 hours of symptom onset to be eligible.		
Non-Randomized Studies			
Amorim et al., 2013[7] 12 community hospitals in an academic telestroke network in the USA NRS – controlled before (12 months preceding telemedicine) and after study.	2,588 patients with possible acute ischemic stroke. 919 patients pre-telemedicine, 1,669 post-telemedicine. Mean age: Pre-TM: 73.9 ±11.5 Post-TM: 73.2 ±13.8 % older than 80 years: Pre-TM: 48.1% Post-TM: 44.2% Hypertension: Pre-TM: 81.5% Post-TM: 72.6% Diabetes: Pre-TM: 29.6% Post-TM: 24.8% Dyslipidemia: Pre-TM: 37% Post-TM: 30.4% Previous Stroke: Pre-TM: 18.5% Post-TM: 24.8%	Telemedicine: real-time videoconferencing, transfer of imaging results. Pre-telemedicine: no formal mechanism for consultation in place.	tPA use, correct treatment usage, time to treatment, mortality, discharge outcomes.

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
Lazaridis et al., 2013[9] One hospital "hub" connected via telemedicine to 12 community "spoke" hospitals (25 to 453 beds, 61 to 187 miles from the hub), in the USA. Determine the safety and effectiveness of tPA and advanced stroke treatment via telemedicine. NRS – prospective cohort	519 of 595 patients who were evaluated using TM and presented with NIHSS>3. Divided by treatment group: no tPA (n = 302), tPA (n = 185), tPA + IA therapy (n = 15); IA therapy only (n = 11), and primary ICH (n = 5). Mean age: no tPA: 67 (SEM 0.86) tPA: 68 (SEM 1.01) tPA + IA: 65 (SEM 3.2) IA: 64 (SEM 3.8) primary ICH: 75 (SEM 5.5) Female no tPA: 47% tPA: 50% tPA + IA: 53% IA: 45% primary ICH: 17%	Telemedicine: computer, LCD screen, camera used for real time video consultation via secure website	Time to treatment, discharge outcomes
Majersik et al., 2012,[8] 24 randomly selected acute care hospitals (from a pool of 61; excluding stroke centres) in the USA; 12 hospitals randomized to the intervention, then were matched to hospitals of similar size. Examine the effect of	243 patients treated with tPA at 12 intervention hospitals 189 without teleconsultation, 54 with teleconsultation Mean age TC 74 ± 12 NTC 70 ± 15 Female: TC 41%	Telephone consultation with an academic stroke team, advice given based on 2005 AHA acute stroke management guidelines. Protocol did not require teleconsultation prior to tPA	In-hospital mortality, symptomatic ICH within 36 hours, adherence with treatment guidelines, use of telemedicine, time to treatment

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
teleconsultation on patients presenting to the ED and treated with tPA NRS – Case series	NTC 53% History of stroke: TC 26% NTC 19% Diabetes: TC 20% NTC 26% History of Hypertension: TC 81% NTC 75%		
Nagao et al., 2012[10] One rural hospital connected via telestroke to an urban hospital with a stroke centre in Australia. To develop a feasible and safe telestroke program in rural Australia in order to provide thrombolysis. NRS - controlled before and after study	145 in the pre-TM group, 130 in the post-TM group. 90 (36 in pre-TM; 54 in TM group) were eligible for thrombolysis and thus included in the analysis. Mean age: Post-TM: 77.5 (23–95) Pre-TM: 78 (51–92) Female: Post-TM: 69% Pre-TM: 44% (P = 0.02) History of stroke: Post-TM: 31% Pre-TM: 31%	Real time videoconference that allowed experts at the stroke centre to consult with remote physicians at the patient's bedside, view CT images, give recommendations regarding thrombolysis therapy.	Treatment times, mortality, symptomatic ICH

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
	Diabetes: Post-TM: 15% Pre-TM: 22% Hypertension: Post-TM: 59% Pre-TM: 67% Hyperlipidemia: Post-TM: 24% Pre-TM: 36%		
Rudd et al., 2012[11] 3 remote emergency departments connected to a central stroke unit in the UK. To describe the efficacy, safety, and process of intravenous thrombolysis for acute ischaemic stroke in the ED setting with remote specialist support through structured telephone consultation. NRS – retrospective case series.	178 patients presenting to ED with stroke symptoms. 84 treated via LSP; 94 via TM Median age: LSP: 76 (47 to 97) TC: 75 (25 to 92)	Telephone consultation: If local stroke physician was not available, EDs contacted a stroke physician on call by telephone. On-call physician had access to imaging via internet-based imaging, guided thrombolysis treatment decisions based on structured clinical information provided by site staff and images but did not speak to the patient or see the patient via videoconference. No telephone consultation: local stroke physician available, made treatment decisions.	Treatment times, functional outcomes, ICH,
Johansson et al., 2011[12] 5 regional hospitals connected, via telemedicine, to a stroke unit in	448 patients; 49 via TM and 399 at stroke centre (47 and 304 analysed)	Telemedicine: remote video-examination with a stroke expert mediated by the regional ED. Completed the NIHSS,	Time to treatment, mortality, functional status

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
Austria. Assess the safety and effectiveness of IV thrombolysis via telemedicine. NRS – retrospective controlled study	Mean age: TM: 67 ± 14 SC: 71 ± 16 (P = 0.062) Female: TM: 34% SC: 50% Diabetes: TM: 8/46 (17%) SC: 57/296 (19%) (P = 0.84) Hypertension: TM: 29/46 (63%) SC: 218/299 (73%) (P = 0.22) Hypercholesterolemia: TM: 21/46 SC: 135/294 (P>0.999)	determined tPA eligibility, viewed CT scans, provided stroke management recommendations. Once tPA was administered, the patient was transferred to a stroke centre.	
Sairanen et al. 2011[13] 5 community hospitals connected to a central, university hospital in Finland. Compare outcomes of patients treated with thrombolysis via telemedicine versus at the central	106 patients in the spoke hospitals, compared with 985 patients at the academic hospital during the same time period. Median age: TM tPA: 72 TM no tPA: 63 (P = 0.006)	Telephone and audiovisual communication between community hospital physicians and the hub when the spoke physician felt the patient was a candidate for thrombolysis. NIHSS performed in conjunction with the hub and spoke physicians, images seen by physicians at both sites,	3 month functional outcomes, mortality, time to treatment, ICH

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
stroke centre. NRS – prospective cohort	SC tPA: 70 (P = 0.136) Female: TM tPA: 56% TM no tPA: 49% (P = 0.629) SC tPA: 46% (P = 0.504)	shared decision making.	
Zaidi et al, 2011[14] 12 spoke hospitals without stroke specialists connected to an academic hub hospital with stroke specialists in the USA. To evaluate the use of tPA delivered via distance consultation vs. in-person consultation. NRS – prospective cohort	351 telemedicine patients evaluated, 83 treated with tPA via TM, 54 treated with tPA at the stroke centre during the same period. Mean age: TM: 71.9 (SD 14.4) SC: 71.9 (SD 14.1) (P = 0.9) Female: TM: 46.9% SC: 56.4% (P = 0.9) Diabetes: TM: 40.9% SC: 30.5% (P = 0.2) Hypertension: TM: 66.2%	Telemedicine: Audio video conferencing, remote viewing of CT/radiology images. When spoke physicians identified a patient as a possible candidate for tPA, hub physician was brought in to consult, aid in performing NIHSS, view imaging findings, review laboratory findings. Hub physician ordered tPA after obtaining consent	90-day functional outcomes, mortality, ICH, time to treatment.

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
	SC: 77.9% (P = 0.1) Atrial Fibrillation: TM: 23.1% SC: 28.8% (P = 0.4)		
Khan et al., 2010[15] Seven remote "spoke" hospitals connected to one academic hub in Alberta. Report 2-year outcomes and experiences of telemedicine program. NRS – retrospective cohort.	210 telestroke patients, 44 considered candidates for thrombolysis and therefore analysed. 34 patients evaluated using TM, 10 using TC. Mean age: TM: 70 (range 21-93) TC: 61 (range 20-86) (P = 0.6) Females: TM: 49% TC: 60% (P = 0.4)	TM: 2-way videoconference system with high definition camera, high resolution LCD monitor. Eligibility for thrombolysis determined based on consultation between hub and spoke physicians. TC: where or when video was not available, telephone consultation was used, CT images viewed at hub when possible.	Time to treatment, mortality, 90-day functional outcomes.
Muengtaweepongsa et al., 2010[16] EDs in Thailand linked to the Thammasat Stroke Center (either within the centre or remotely) To report feasibility and safety of the administration of tPA in patients with acute ischemic stroke using remote	458 patients with acute ischemic stroke, 100 received tPA (tPA rate 21%) Patient characteristics NR	DICOM transfer of CT images via secure online server, telephone consultation from stroke neurologists to EDs for the transfer of clinical details	IV tPA rate, time to treatment, ICH, 90-day functional outcomes, mortality

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
radiology interpretation and telephone consultation. NRS – retrospective cohort			
Pervez et al., 2010[17] 33 “spoke” hospitals connected to a hub hospital via telemedicine in the USA. To compare outcomes of patients who received telemedicine-guided tPA at a remote centre vs patients who received tPA at a stroke centre; to compare telestroke with telephone-only. Most remote patients transferred to stroke centre after tPA treatment. NRS – retrospective cohort.	296 patients who received IV tPA; 115 treated via TM at a regional centre, 181 at the hub stroke centre. Mean age: TM: 73.6±12.4 SC: 71.5±14.7 (P = 0.05) Females: TM: 51.3% SC: 53% (P = 0.77) Diabetes: TM: 25.2% SC: 16.6% (P = 0.07) Hypertension: TM: 71.3% SC: 65.3% (P = 0.27) Dyslipidemia: TM: 40.0% SC: 29.8%	Telemedicine: two way videoconferencing, remote viewing of imaging, guidance from the hub physician with respect to treatment decisions. Stroke Centre: patients treated by stroke experts at the hub hospital	Time to treatment, ICH, mortality, ambulatory at discharge

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
	(P = 0.07) History of stroke/TIA: TM: 24.4% SC: 15.5% (P = 0.06) History of CAD or MI: TM: 27.0% SC: 26.0% (P = 0.85)		
Audebert et al., 2009[18] 5 community hospitals with remote telestroke assistance compared to 5 matched hospitals without telestroke assistance in Germany. (TEMPiS trial) Report follow-up results 12 and 30 months after acute stroke. NRS – follow-up of prospective controlled study	3,060 patients; 1,938 in TM hospitals, 1,122 in control hospitals. For death and institutional care outcomes: 12 month follow-up: 97.2% 30 month follow-up: 95.9% For death and dependency outcomes: 12 month follow-up: 96.5% 30 month follow-up: 95.7% Diabetes: TM: 22% no-TM: 29% Previous stroke: TM: 17% No-TM: 23%	Telemedicine: audiovisual consultation assistance from stroke experts in an academic hub. Images were viewed by remote physician, remote expert helped to guide examination of patients and treatment decisions. No telemedicine: no official access to remote stroke experts.	Death and dependency: defined by death, institutional care, or disability (Barthel index <60 or Rankin scale<3).
Pedragosa et al., 2009[19]	399 patients; 201 pre-TM, 198	TM: videoconference system that	Functional outcomes (reduction in

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
Community hospital without stroke specialist, compared pre- and post- introduction of telestroke with an urban centre hospital with stroke experts in Spain. To examine the impact of the introduction of a telestroke program. NRS – before and after	post-TM. 9 received tPA pre-TM, 19 received tPA post-TM Mean age (of tPA patients): pre-TM: 68 (SD 13) post-TM: 78 (SD 8) (P = 0.08)	allowed physicians at the community hospital to communicate with those at the stroke centre. Stroke centre physicians could see the patient, imaging information was transferred. Community physicians were instructed to communicate with the TM equipment if a patient presented within 6 hours of stroke onset. Thrombolytic therapy was initiated when appropriate. Pre-TM: physicians at community hospital advised to transfer stroke patients who were within 6 hours of onset or who had worsening symptoms to the stroke centre.	NIHSS), time to treatment
Switzer et al., 2009[20] 9 community “spoke” hospitals connected to an academic “hub” hospital with a stroke centre in the USA. To document the outcomes of the first 50 patients receiving tPA via telemedicine in the telestroke network compared with the results of an ED that does not use telestroke.	Patients who received tPA via TM guidance (n = 50) or in the hub ED (n = 26) Mean age: 63 (unclear if this was all patients or TM only) Females: 60% (unclear if this was all patients or TM only)	TM: two way videoconference between physicians at the spoke hospitals and stroke experts at the hub hospital. Hub physicians were able to see the patient to participate in conducting assessments, laboratory values and imaging results were able to be viewed by the hub physicians as well. no-TM: ED at the hub hospital who did not consult via	Treatment time, ICH, discharge functional outcomes

Table 3: Characteristics of the Included Randomized and Non-Randomized Studies			
Author, Year, Setting, Objective; Type of Study	**Patient Characteristics**	**Details of the Distance Stroke/Telemedicine Program; Details of Comparators**	**Main Outcomes**
NRS – retrospective controlled		telemedicine	

AHA = American Heart Association; CAD = coronary artery disease; CT = computed tomography; DICOM = digital imaging and communications in medicine; ED = emergency department; IA = intra-arterial; ICH = intracranial hemorrhage; IV = intravenous; LSP = local stroke physician; MI = myocardial infarction; NIHSS = National Institutes of Health Stroke Scale; NTC = non-telephone consultation; RCT = randomized controlled trial; SC = stroke centre; TC = telephone consultation; TM = telemedicine; tPA = tissue plasminogen activator; USA = United States of America

[a] Of patients at the spoke/community hospitals only

[b] Telemedicine vs. Telephone-only consultation

APPENDIX 4: Summary of Critical Appraisal

Table 4: Critical Appraisal Details of the Included HTA and SR Using AMSTAR[4]

Strengths	Limitations
Johansson & Wild, 2010[2,21,22]	
'A priori' design partially provided. Duplicate study selection and data extraction was done. Was a comprehensive literature search performed – 4 databases, dates provided, hand searching performed. Characteristics of the included studies partially provided. Were the methods used to combine the findings of studies appropriate – too much heterogeneity to pool studies, therefore narrative review presented.	Not clear if the status of publication (i.e. grey literature) used as an inclusion criterion. List of included and excluded studies not provided. Scientific quality of the included studies not presented. Scientific quality of the included studies not used in formulating conclusions. Was the likelihood of publication bias not assessed (or not presented). Funding information provided, but no conflict of interest statement included.
Deshpande et al., 2008[3]	
An 'a priori' design was provided. Duplicate study selection and data extraction occurred. A comprehensive literature search performed – multiple databases, dates provided, hand-search performed. The status of publication was used as an inclusion criterion – case series excluded. A list of studies (included and excluded) was provided. The characteristics of the included studies were provided. The scientific quality of the included studies was assessed and documented. The scientific quality of the included studies was used appropriately in formulating conclusions. The methods used to combine the findings of studies were appropriate – too much heterogeneity to pool studies, narrative review presented. The likelihood of publication bias was not assessed but the exclusion of unpublished studies was mentioned as a limitation. Conflict of interest statement was included.	No major limitations.

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]

Strengths	Limitations
Randomized Controlled Trials	
Demaerschalk et al., 2010[6]	
REPORTING Hypothesis, main outcomes, characteristics of patients clearly described. Interventions described in minor detail in the current publication, full detail in companion publications. Distribution of principal confounders in each group	INTERNAL VALIDITY (bias) Patients were not blinded to the type of consultation. POWER Unclear if study had sufficient power to detect a

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
clearly described. Main findings clearly described. Estimates of random variability provided. Some adverse events reported. Characteristics of patients unable to participate reported; no patients lost to follow-up. Actual probability values reported for the main outcomes. EXTERNAL VALIDITY Subjects asked to participate and subjects who ultimately participated were likely representative of the entire population. Staff, places, and facilities where the patients were treated, likely representative of the treatment the majority of patients receive. INTERNAL VALIDITY (bias) Those measuring the main outcomes of the intervention were blinded. Data dredging did not appear to occur. Statistical tests used to assess the main outcomes appropriate. Compliance with the intervention reliable. The main outcome measures used were accurate INTERNAL VALIDITY (confounding/selection bias) Patients in the different intervention groups were recruited from the same population and over the same period of time. Subjects were randomized to intervention groups Randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable. Confounding did not appear to be an issue in this study Patient follow-up described	clinically important effect where the probability value for a difference being due to chance is less than 5%; power calculation not presented.
Non-Randomized Studies	
Amorim et al., 2013[7]	
REPORTING The objectives of the study are clearly described. The main outcomes, patient characteristics, and interventions are clearly described. The distributions of principal confounders in each group of subjects are clearly described. The main findings of the study clearly described. Estimates of the random variability in the data for the main outcomes provided. Some important adverse events reported. Actual probability values been reported.	REPORTING Characteristics of patients lost to follow-up not clearly described. INTERNAL VALIDITY (bias) No attempt at blinding study subjects. Unclear if an attempt made to blind those measuring the main outcomes of the intervention INTERNAL VALIDITY (confounding/selection bias) Subjects were not randomized to intervention

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
EXTERNAL VALIDITY Subjects asked to participate and those who did participated likely representative of the population of patients who present with likely ischemic stroke. Staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive in the area in which the study occurred. INTERNAL VALIDITY (bias) Data dredging not likely to have occurred. Statistical tests used to assess the main outcomes appropriate. Compliance with the intervention reliable. Were the main outcome measures used accurate. INTERNAL VALIDITY (confounding/selection bias) Patients were recruited from the same population. Patients within each treatment group were recruited over the same period of time, though due to the before-after, the different intervention groups were recruited at different periods of time. Patient disposition was reported	groups. Analyses were presented as unadjusted values. POWER Unclear if study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%.
Lazaridis et al., 2013[9]	
Objective of the study clearly described. Main outcomes to be measured clearly described. Interventions of interest clearly described. Are the main findings of the study clearly described. Study provides estimates of the random variability in the data for the main outcomes. Some important adverse events that may be a consequence of the intervention been reported – technical difficulties not reported. EXTERNAL VALIDITY Subjects asked to participate in the study likely representative of the entire population from which they were recruited. Subjects who were prepared to participate likely representative of the entire population from which they were recruited. Staff, places, and facilities where the patients were treated, likely representative of the treatment the majority of patients receive. INTERNAL VALIDITY (bias) Data dredging likely did not occur. Statistical tests used to assess the main outcomes appropriate.	REPORTING Are the characteristics of the patients included in the study partially described – key comorbidity information missing. Distributions of principal confounders in each group of subjects to be compared partially. The characteristics of patients lost to follow-up not described. Actual probability values were not reported. INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they received. No attempt made to blind those measuring the main outcomes of the intervention. INTERNAL VALIDITY (confounding/selection bias) Subjects not randomized to intervention groups. No adjustment for confounding in the analyses from which the main findings were drawn. Losses of patients to follow-up not taken into account.

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
Compliance with the interventions reliable. Main outcome measures used accurate. POWER Study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%.	
Majersik et al., 2012[8]	
REPORTING Objective clearly described – companion publication contained further detail. Main outcomes clearly described Interventions somewhat clearly described Distributions of confounders clearly described Main findings clearly described, characteristics of patients lost to follow-up described. EXTERNAL VALIDITY Subjects asked to participate in the study likely representative of the population from which they were recruited and those who participated likely representative of the population. Several distance sites were used, likely encompassed the places, facilities, and staff from which the majority of patients would receive treatment. INTERNAL VALIDITY (bias) Those measuring the main outcomes of the intervention were blinded The time period between the intervention and outcome was the same for all patients, patients were recruited over the same period of time. Possible confounding factors were mentioned, however were not adjusted for – though there did not seem to be the need for adjustment. Compliance with the intervention was reliable The main outcome measures used were accurate. Few statistical tests performed – descriptive statistics most common. No losses to follow-up Does not appear that data dredging occurred.	REPORTING Characteristics of patients not clearly described Estimates of the random variability in the data for the main outcomes not clearly reported. Some important adverse events that may be a consequence of the intervention been reported Probability values were not reported for the main outcomes. INTERNAL VALIDITY (bias) Study subjects were not blinded to the intervention they received INTERNAL VALIDITY (confounding/selection bias) Study subjects were not randomized to intervention groups POWER Power calculation not presented.
Nagao et al., 2012[10]	
REPORTING Objective of the study clearly described. Main outcomes to be measured clearly described in the methods section. Characteristics of the patients included in the study relatively clearly described. Interventions of interest clearly described. Distributions of principal confounders in each group	REPORTING Characteristics of patients lost to follow-up not clear. EXTERNAL VALIDITY Significantly more female patients were represented in the group of patients who were eligible for thrombolysis treatment and were

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
of subjects to be compared clearly described. Main findings are relatively clearly described – not all outcomes presented for all patients. Estimates of the random variability in the data for the main outcomes presented. Most important adverse events that may be a consequence of the intervention been reported, though not for all patients. Actual probability values reported for the main outcomes reported. EXTERNAL VALIDITY Subjects asked to participate in the study likely representative of the entire population from which they were recruited. Staff, places, and facilities where the patients were treated, likely representative of the treatment the majority of patients receive. INTERNAL VALIDITY (bias) Statistical tests used to assess the main outcomes appropriate. Compliance with the intervention reliable. The main outcome measures used were accurate. INTERNAL VALIDITY (confounding/selection bias) Patients in different intervention groups were recruited from the same population. The study subjects within each group were recruited over the same period of time; the intervention group was recruited in the 12 months following the 12 month recruitment for the non-intervention group. Losses of patients to follow-up partially taken into account.	included in the analysis. INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. Unclear if an attempt made to blind those measuring the main outcomes of the intervention. Not clear if any of the results of the study were based on “data dredging.” INTERNAL VALIDITY (confounding/selection bias) Study subjects were not randomized to intervention groups. Not clear if there was adequate adjustment for confounding in the analyses from which the main findings were drawn. POWER Unclear if the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%; power calculation not presented.
Rudd et al., 2012[11]	
REPORTING Objective of the study clearly described. Main outcomes to be measured clearly described methods section. Interventions of interest clearly described. Main findings of the study clearly described. Interquartile ranges provided for the main outcomes. Most important adverse events that may be a consequence of the intervention been reported. Characteristic of the patients included in the study somewhat clearly described. EXTERNAL VALIDITY Were the subjects asked to participate and those	REPORTING Distributions of principal confounders in each group of subjects to be compared partially described. Probability values were not reported. INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. Not clear if attempt made to blind those measuring the main outcomes of the intervention. INTERNAL VALIDITY (confounding/selection bias) Subjects were not randomized to intervention groups. Unclear if there adequate adjustment for

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
who did participate in the study likely representative of the entire population from which they were recruited. Staff, places, and facilities where the patients were treated, partially representative of the treatment the majority of patients receive – many remote sites do not have a stroke specialist available part of the time. INTERNAL VALIDITY (bias) Not likely that data dredging occurred. Time period between the intervention and outcome the same for cases and controls. Statistical tests used to assess the main outcomes appropriate. Compliance with the intervention reliable. Main outcome measures used were accurate. INTERNAL VALIDITY (confounding/selection bias) Were the patients in the different intervention groups were recruited from the same population and over the same period of time. Losses of patients to follow-up taken into account.	confounding in the analyses from which the main findings were drawn. POWER Unclear if the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%. Power calculation not provided.
Johansson et al., 2011[12]	
REPORTING Objectives of the study clearly described. Main outcomes to be measured clearly described. Characteristics of the patients included in the study clearly described. Interventions of interest clearly described. Distributions of principal confounders in each group of subjects clearly described. Main findings of the study clearly described. Study provides estimates of the random variability in the data for the main outcomes. Most important adverse events that may be a consequence of the intervention been reported. Actual probability values been reported. EXTERNAL VALIDITY Subjects asked to participate in the study and those who participated were likely representative of the entire population from which they were recruited. The staff, places, and facilities where the patients were treated, were likely representative of the treatment the majority of patients receive. INTERNAL VALIDITY (bias) Not likely that any of the results of the study were based on data dredging.	INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. Not clear if attempt made to blind those measuring the main outcomes of the intervention. Characteristics of patients lost to follow-up not clearly described INTERNAL VALIDITY (confounding/selection bias) The patients in different intervention groups were recruited from the somewhat different populations – one urban, one rural. Unknown if this would have an effect on the outcomes. Study subjects not randomized to intervention groups. Unclear if there adequate adjustment for confounding in the analyses from which the main findings were drawn. POWER Unclear if study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%.

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
The time period between the intervention and outcome the same for the groups. Statistical tests used to assess the main outcomes were appropriate. Compliance with the intervention was reliable. The main outcome measures used were accurate. INTERNAL VALIDITY (confounding/selection bias) Study subjects in different intervention groups recruited over the same period of time. Losses of patients to follow-up taken into account.	
Sairanen et al. 2011[13]	
REPORTING Objective of the study clearly described. Main outcomes to be measured clearly described in the methods section. The interventions of interest are clearly described. The main findings of the study are clearly described. Estimates of the random variability in the data for the main outcomes provided. Characteristics of patients lost to follow-up have been partially described. Actual probability values been reported for the main outcomes. EXTERNAL VALIDITY Subjects asked to participate in the study likely representative of the entire population from which they were recruited. Subjects who were prepared to participate were likely representative of the entire population from which they were recruited. Staff, places, and facilities where the patients were treated, likely representative of the treatment the majority of patients receive. INTERNAL VALIDITY (bias) Data dredging likely did not occur The time period between the intervention and outcome was the same for all participants. Were the statistical tests used to assess the main outcomes appropriate? Compliance with the intervention was mostly reliable – some question about data collection. Main outcome measures used accurate. INTERNAL VALIDITY (confounding/selection bias) The patients in different intervention groups were recruited from approximately the same population – unclear if urban and rural patients would differ.	REPORTING Characteristics of the patients included in the study are partially described; key comorbidities missing. Distributions of principal confounders in each group of subjects are not clearly described. Not all important adverse events that may be a consequence of the intervention been reported. INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. No attempt made to blind those measuring the main outcomes of the intervention. INTERNAL VALIDITY (confounding/selection bias) The study subjects in different intervention groups were not recruited over the same period of time – telemedicine from 2007 to 2009, registry from 1998 to 2008. Study subjects not randomized to intervention groups. Unclear if there adequate adjustment for confounding in the analyses from which the main findings were drawn. POWER Unclear if the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%.

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
Losses of patients to follow-up taken into account.	
Zaidi et al, 2011[14]	
REPORTING Objective of the study clearly described. Main outcomes to be measured clearly described. Characteristics of the patients included in the study clearly described. Interventions of interest clearly described. Distributions of principal confounders in each group of subjects clearly described. Main findings of the study clearly described. Study provides estimates of the random variability in the data for the main outcomes. Most important adverse events that may be a consequence of the intervention been reported – technical difficulties not reported. EXTERNAL VALIDITY Subjects asked to participate in the study likely representative of the entire population from which they were recruited. Subjects who were prepared to participate likely representative of the entire population from which they were recruited. Staff, places, and facilities where the patients were treated likely representative of the treatment the majority of patients receive. INTERNAL VALIDITY (bias) Data dredging likely did not occur. The time period between the intervention and outcome was the same in both groups. Statistical tests used to assess the main outcomes appropriate. Compliance with the intervention reliable. Main outcome measures used accurate. INTERNAL VALIDITY (confounding/selection bias) The patients in different intervention groups were recruited from a similar population – unclear if rural or urban would make a difference. Study subjects in different intervention groups recruited over the same period of time. Losses of patients to follow-up mentioned.	REPORTING Characteristics of patients lost to follow-up not clearly described. Actual probability values been reported. INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. No attempt made to blind those measuring the main outcomes of the intervention. INTERNAL VALIDITY (confounding/selection bias) Study subjects not randomized to intervention groups. Unclear if there was adequate adjustment for confounding in the analyses from which the main findings were drawn. POWER Unclear if study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%.
Khan et al., 2010[15]	
REPORTING Objective of the study clearly described as are the outcomes, characteristics of patients, and interventions of interest. Main findings of the study clearly described.	REPORTING Distributions of principal confounders in each group of subjects to be compared not clearly described. Not all important adverse events that may be a consequence of the intervention been reported.

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
Study provides estimates of the random variability in the data for the main outcomes. Characteristics of patients lost to follow-up well-described. Actual probability values been reported. EXTERNAL VALIDITY Subjects asked to participate in the study likely representative of the entire population from which they were recruited. Subjects who were prepared to participate likely representative of the entire population from which they were recruited. Staff, places, and facilities where the patients were treated, likely representative of the treatment the majority of patients would receive. INTERNAL VALIDITY (bias) Not likely that results were due to data dredging. The time period between the intervention and outcome was the same for cases and controls. Statistical tests used to assess the main outcomes appropriate. Compliance with the intervention reliable. Main outcome measures used accurate. INTERNAL VALIDITY (confounding/selection bias) The patients in different intervention groups were recruited from a population that was likely the same. Study subjects in different intervention groups recruited over the same period of time. Losses of patients to follow-up taken into account.	INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. No attempt made to blind those measuring the main outcomes of the intervention. INTERNAL VALIDITY (confounding/selection bias) Study subjects were not randomized to intervention groups. Unclear if there was adequate adjustment for confounding in the analyses. POWER Unclear if the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%.
Muengtaweepongsa et al., 2010[16]	
REPORTING Aim of the study clearly described. Main outcomes to be measured clearly described in the methods section. Interventions of interest clearly describe. Are the main findings of the study somewhat clearly described. Some important adverse events that may be a consequence of the intervention reported – technical difficulties not mentioned. EXTERNAL VALIDITY Staff, places, and facilities where the patients were treated, likely representative of the treatment the majority of patients receive in the trial location. INTERNAL VALIDITY (bias)	REPORTING Characteristics of the patients included in the study not clearly described. Distributions of principal confounders in each group of subjects to be compared not clearly described. Estimates of the random variability in the data for the main outcomes not provided. Characteristics of patients lost to follow-up not described. No probability values reported. EXTERNAL VALIDITY Unclear if the subjects asked to participate in the study representative of the entire population from which they were recruited. Unclear if subjects who were prepared to participate representative of the entire population

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
Not likely that any of the results of the study were based on data dredging. Patients had the same follow-up time. Compliance with the intervention/s reliable? Main outcome measures used were accurate. INTERNAL VALIDITY (confounding/selection bias) Losses of patients to follow-up mentioned.	from which they were recruited. INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. No attempt made to blind those measuring the main outcomes of the intervention. Statistical tests used to assess the main outcomes not presented. INTERNAL VALIDITY (confounding/selection bias) Study subjects not randomized to the intervention groups. Unclear/unlikely there adequate adjustment for confounding in the analyses from which the main findings were drawn. POWER No power calculation presented.
Pervez et al., 2010[17]	
REPORTING Objective of the study clearly described. Main outcomes to be measured clearly described in methods. Characteristics of the patients included in the study clearly described. Interventions of interest clearly described. Distributions of principal confounders in each group of subjects to be compared clearly described. Main findings of the study clearly described. Study provides estimates of the random variability in the data for the main outcomes. Some important adverse events that may be a consequence of the intervention been reported – no mention of technical difficulties. Actual probability values been reported. EXTERNAL VALIDITY Subjects asked to participate in the study likely representative of the entire population from which they were recruited. Subjects who were prepared to participate likely representative of the entire population from which they were recruited – though they may be slightly older than the norm, unclear. Staff, places, and facilities where the patients were treated, likely representative of the treatment the majority of patients receive – both rural and urban. INTERNAL VALIDITY (bias) Data dredging likely did not occur.	REPORTING Characteristics of patients lost to follow-up not well described. INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. No attempt made to blind those measuring the main outcomes of the intervention. INTERNAL VALIDITY (confounding/selection bias) Study subjects not randomized to intervention groups.

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
The time period between the intervention and outcome the same for all groups. Statistical tests used to assess the main outcomes appropriate. Compliance with the intervention reliable. Main outcome measures used were accurate. INTERNAL VALIDITY (confounding/selection bias) The patients in different intervention groups recruited from a similar population – unclear if urban/rural would affect outcomes. Study subjects in different intervention groups were recruited over the same period of time. Adequate adjustment for confounding in the analyses from which the main findings were drawn. Losses of patients to follow-up taken into account. POWER Study likely had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%, however, power calculation not reported.	
Audebert et al., 2009[18]	
REPORTING Objective of the study clearly described. Main outcomes to be measured clearly described. Interventions of interest clearly described. Distributions of principal confounders in each group of subjects clearly described. Main findings of the study clearly described. Estimates of the random variability in the data for the main outcomes provided. Actual probability values have been reported. EXTERNAL VALIDITY Subjects asked to participate in the study likely representative of the entire population from which they were recruited. Subjects who were prepared to participate likely representative of the entire population from which they were recruited? Staff, places, and facilities where the patients were treated likely representative of the treatment the majority of patients receive – control and intervention hospitals were matched. INTERNAL VALIDITY (bias) Attempt made to blind those measuring the main outcomes of the intervention; not all outcome assessors ended up being blinded. Unlikely data dredging occurred.	REPORTING Characteristics of the patients included in the study not clearly described in the included publication, but are included in a companion publication. Important adverse events that may be a consequence of the intervention not reported in this publication, likely included in a companion publication. The characteristics of patients lost to follow-up not described in detail. INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. INTERNAL VALIDITY (confounding/selection bias) Study subjects not randomized to intervention groups.

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
The time period between the intervention and outcome the same for both groups. Statistical tests used to assess the main outcomes appropriate. Compliance with the interventions reliable. Main outcome measures used accurate. INTERNAL VALIDITY (confounding/selection bias) Patients in different intervention recruited from similar populations – control hospitals were matched to the intervention hospitals. Study subjects in different intervention groups were recruited over the same period of time. Adequate adjustment for confounding in the analyses from which the main findings were drawn. Losses of patients to follow-up taken into account. POWER The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%	
Pedragosa et al., 2009[19]	
REPORTING Objective of the study clearly described. Main outcomes to be measured patially described. The interventions of interest clearly described. The distributions of some principal confounders in each group of subjects to be compared described. Main findings of the study clearly described. Study provides estimates of the random variability in the data for the main outcomes. Actual probability values been reported. EXTERNAL VALIDITY The staff, places, and facilities where the patients were treated were likely representative of the treatment the majority of patients receive. INTERNAL VALIDITY (bias) Not likely that results of the study were based on "data dredging." The time period between the intervention and outcome was the same for cases and controls The statistical tests used to assess the main outcomes were appropriate. The compliance with the interventions was reliable. The main outcome measures used were accurate. INTERNAL VALIDITY (confounding/selection bias) The patients in different intervention groups were recruited from the same population.	REPORTING Characteristics of the patients included in the study not clearly described. Not all important adverse events that may be a consequence of the intervention been reported. Characteristics of patients lost to follow-up were not described. EXTERNAL VALIDITY Unclear if subjects asked to participate in the study representative of the entire population from which they were recruited – sex not reported, not all characteristics reported. Unclear if subjects who were prepared to participate representative of the entire population from which they were recruited – sex not reported, not all characteristics reported. INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. No attempt made to blind those measuring the main outcomes of the intervention. INTERNAL VALIDITY (confounding/selection bias) The study subjects in different intervention groups were not recruited over the same period of time – due to being a before/after study. Study subjects were not randomized to intervention

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
	groups. Not clear if there was adequate adjustment for confounding in the analyses from which the main findings were drawn? Losses of patients to follow-up not taken into account. POWER Unclear if the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%.
Switzer et al., 2009[20]	
REPORTING Objective of the study clearly described. Outcomes partially clearly described Interventions of interest are clearly described. Main findings of the study clearly described. Study provides some estimates of the random variability in the data for the main outcomes. Actual probability values been reported. EXTERNAL VALIDITY Staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive in their particular regions. INTERNAL VALIDITY (bias) Not likely that data dredging occurred. Compliance with the interventions reliable. Main outcome measures used accurate. The statistical tests used to assess the main outcomes appropriate – authors mentioned limitations of the tests they performed. INTERNAL VALIDITY (confounding/selection bias) Patients in different intervention were recruited from a similar population – unclear if there would be differences between the rural and urban populations. The subjects in different intervention groups were recruited over the same period of time.	REPORTING Characteristics of the patients included are partially described – only information for the intervention group is provided, not complete. Distributions of principal confounders in each group of subjects not clearly described. Not all important adverse events that may be a consequence of the intervention been reported. Characteristics of patients lost to follow-up not clearly described. EXTERNAL VALIDITY Unclear if subjects asked to participate in the study representative of the entire population from which they were recruited. Unclear if subjects who were prepared to participate representative of the entire population from which they were recruited. INTERNAL VALIDITY (bias) No attempt made to blind study subjects to the intervention they have received. No attempt made to blind those measuring the main outcomes of the intervention. The time period between the intervention and outcome the same for cases and controls. INTERNAL VALIDITY (confounding/selection bias) Study subjects not randomized to intervention groups. Not clear if there was adjustment for confounding in the analyses from which the main findings were drawn. Losses of patients to follow-up not taken into account. POWER Unclear if the study had sufficient power to detect a

Table 5: Critical Appraisal Details of the Included Randomized and Non-Randomized studies using the Downs and Black Checklist[5]	
Strengths	**Limitations**
	clinically important effect where the probability value for a difference being due to chance is less than 5%.

APPENDIX 5: Summary of Study Findings

Table 6: Summary of Results of the Included HTA and SR				
Number of consultations	**Time to treatment (minutes)**	**% patients who received tPA**	**Mortality**	**Other events**
Deshpande et al., 2008[3]				
NR	Door to needle: Video: 62.9 to 106 (reported in 4 studies) Onset to treatment: Video: 23% treated within 90 min, 60% within 120 min. (1 study)	Increase in thrombolysis treatment after introduction of distance consultation reported in 4 studies – from 10 cases to 86 in 1 study (VC), 72% increase in 1 study (TC), from 0.8% to 4.3% (P < 0.001) in 1 study (VC), from 0% to 5.6% in 1 study (VC).	6 month mortality (1 RCT): TC: 34.0% TM: 24.7% (P <0.025).	"Poor outcomes" after 90 days (1 study): TM 44%; No TM 54% (P<0.025) and TM independently reduced the probability of a poor outcome (OR 0.62, 95% CI 0.52 to 0.74; P <0.0001) TM associated with the absence of tPA-related complications in 2 studies. 2 studies included measures of satisfaction. Physicians felt care was improved for 95% of patients in one study, one study reported that patients and staff viewed TM positively. Diagnostic accuracy (1 study): TC-only: 63.8% VC: 87.7% TC + transfer of images: 89.1% (P < 0.0005 for TC-only vs. VC and TC-only vs. TC + transfer of images)
Johansson & Wild, 2010[2,21,22]				
tPA studies: Ranged from 24 to 2,182 for tPA treatment	Mean onset to hospital: 54 to 71 Mean door to tPA administration: Total: 76 to 106 Video: 68 to 106 Telephone: 105 (reported in 1 study	Total: 729 patients (N not reported) Ranged from 1.3% to 30% in studies reporting tPA administration.	Telephone tPA patients: 0% to 39% Video tPA patients: 0% to 50%[a] 2 studies reported in-hospital mortality both examined	1 study reported diagnostic accuracy and correct treatment decision making: Diagnostic accuracy was 87.7% for video vs. 63.8 % in the telephone group (P =.001) Correct decision making occurred 98% of the time for video, 82% for telephone (OR 10.9, 95% CI, 2.7–44.6; P = .0009)

Table 6: Summary of Results of the Included HTA and SR				
Number of consultations	**Time to treatment (minutes)**	**% patients who received tPA**	**Mortality**	**Other events**
	only) Mean onset to tPA administration: Total: 122[b] to 165 Video: 122 to 135.5 Telephone: 119 to 165		video consultation for tPA administration: 10.4% and 3.5%	1 included study found better health outcomes in patients treated remotely than in conventionally treated patients. 3 studies included a measure of satisfaction with the telemedicine – patients and healthcare providers were satisfied with telemedicine.

CI = confidence interval; min = minutes; NR = not reported; OR = odds ratio; TC = telephone consultation; TM = telemedicine; tPA = tissue plasminogen activator; VC = videoconferencing;
[a]represented 1 of 2 patients receiving tPA
[b]as reported in the main publication; supplementary tables indicate low range to be 119

Table 7: Summary of Results of the Included Randomized and Non-Randomized Studies						
First author, Comparison; Stroke severity	**Time to treatment (minutes, mean unless specified)**	**Correct Utilization of Treatment Options**	**Mortality**	**Functional Outcomes**	**Other Adverse Events**	**Other**
Randomized Controlled Trials						
Demaerschalk et al., 2010[6] Telemedicine vs. telephone consultation Mean pre-treatment NIHSS: TM: 7.1±5.7 TC: 7.6±6.7	Onset to door: TM: 88.2 ± 127.8 TC: 74.1 ± 34.5; (P = 0.098) Onset to treatment decision: TM: 188.2 ± 138.2 TC: 164.8 ± 28.6 (P = 0.067) Onset to tPA	TM: 85% telemedicine TC: 89% (P > 0.999)	TC: 1 (4%) TM: 3 (11%) (P = NS) In patients receiving tPA: TM: 0 TC: 1 (P = NS)	% patients with 90 day BI (95-100)" TM: 59% TC: 58% (P = 0.77) % patients with 90 day mRS (dichotomized 0-1): TM: 46% TC: 48% (P = 0.61)	NR	tPA use the same in each group – 30% Technical problems noted:[a] TM: 74% TC: 0%

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	treatment: TM (n=8): 164.6 ± 31.7 TC (n=8): 170.5 ± 17.2 (P = 0.798) Door to treatment decision: TM: 100.5 ± 28.4 TC: 90.7 ±27.9 (P = 0.115)					
Non-Randomized Studies						
Amorim et al., 2013[7] Pre-TM vs. Post-TM Median pre-treatment NIHSS: Pre-TM: 8 Post-TM: 12 (P = 0.38)	Onset-to-door: Pre-TM: 61.9 ± 37.2 Post-TM: 56.2 ± 29.1 (P=0.4) Onset-to-treatment: Pre-TM: 129.8 ±34 Post-TM: 124.4 ± 34 (P = 0.49) Door-to-treatment: Pre-TM: 74.2 ±32.1	Incorrect treatment decision: Pre-TM: 0.2% Post-TM: 0.3% (P = 0.7)	In-hospital: Pre-TM: 7.4% Post-TM: 10.9% (P = 0.59)	NR	Symptomatic ICH: Pre-TM: 3.7% Post-TM: 0.9% (P = 0.34)	tPA administration: Pre-TM: 2.8% Post-TM: 6.8% (P<0.001)

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	Post-TM: 74 ±29.1 (P = 0.98)					
Lazaridis et al., 2013[9] Telemedicine – outcome based on treatment type compared. Mean pre-treatment NIHSS: no tPA: 8 (5-14) tPA: 10 (6-17) (no tPA vs tPA: P ≤ 0.01) tPA + IA: 18 (8-20) IA: 15 (5-20) primary ICH: 13 (10-20)	Onset to arrival: no tPA: 78 (40-158) tPA: 60 (40-90) (no tPA vs tPA: P ≤ 0.01) tPA + IA: 38 (20-40) IA: 140 (30-220) primary ICH: 20 (25-45) Onset to tPA: no tPA: NA tPA: 152 (120-193) tPA + IA: 147 (107-179) IA: NA primary ICH: NA Door to tPA: no tPA: NA tPA: 90 (69-113) tPA + IA: 84 (75-120) IA: NA primary ICH: NA	NR	At discharge: no tPA: 2.7% tPA: 5.4% tPA + IA: 13.3% IA: 18.2% primary ICH: 0%	NR	Symptomatic ICH: no tPA: 0% tPA: 1.6% (no tPA vs tPA: P ≤ 0.01) tPA + IA: 6.7% IA: 0% primary ICH: 0%	Most common reason for not receiving tPA: outside the treatment window
Majersik et al., 2012[8]	Onset to arrival:	NR	TC: 3 (5.6%)	NR	Symptomatic ICH	Treatment

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Telephone consultation (n =54) vs. no telephone consultation (n = 189) Mean pre-treatment NIHSS scores: TC: 12 (8–18); NTC 10 (6–16)	TC 58 min (42–71) NTC 60 min (38–87) Door to treatment TC: 85 min (63–106) NTC: 85 min (66–108)		NTC: 25 (13.2%)		within 36 hours: TC: 3 (5.6%) NTC: 13 (7.3%)	guideline deviation (excluding timing) TC: 7 (13%) NTC: 18 (9.5%)
Nagao et al., 2012[10] Pre-TM vs Post-TM who were eligible for thrombolysis treatment Mean pre-treatment NIHSS: Post-TM: 8.4 ± 7.4 Pre-TM: NR	Median onset to arrival: Post-TM: 107 (0–228) Pre-TM: 115 (15–220) Median door to CT: Post-TM: 70 (0–600) Pre-TM: 80 (20–240) (P = 0.66)	NR	Post-TM group, for those where TM was used (n = 24) vs. not used (n = 30): TM used: 13% TM not used: 10% (P = 0.6)	NR	Post-TM group, for those where TM was used (n = 24) vs. not used (n = 30) Further stroke: TM used: 8.3% TM not used: 0% ICH: TM used: 0 TM not used: 0	Technical difficulties during TM consultation: 6 occurrences 33% of eligible patients received thrombolysis therapy – compared to 0% when TM was not available.
Rudd et al., 2012[11] Consultation with LSP vs. telephone consultation (all	Door to needle, median (IQR): LSP: 65 (46 to 84) TC: 73 (51 to 95)	NR	90 day mortality: LSP: 18.1% TC: 19.6%	% patients with mRS 0-1 after 90 days: LSP: 36% TC: 31%	ICH: LSP: 14.3% TC: 7.4%	Tendency for the LSPs to treat patients with more pre-stroke disability

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patients received thrombolysis) Median pre-treatment NIHSS:[c] LSP: 13.5 (3 to 24) TC: 14 (4 to 24)				% patients with mRS 4-5[d] after 90 days: LSP: 17% TC: 20% Median 7-day NIHSS reduction:[e] LSP: 7.5 (4 to 11) TC: 7 (3 to 11) P values not reported		
Johansson et al., 2011[12] TM vs SC treatment Mean pre-treatment NIHSS: TM: 9.9 (SD 5.2) SC: 10.4 (SD 5.9) (P = 0.73)	Onset to door:[f] TM: 231 (SD 57) SC: 108 (SD 72) (P<0.001) Onset to tPA treatment:[g] TM: 113 (SD 40) SC: 122 (SD 47) (P = 0.26)	NR	In-hospital: TM: 4 SC: 8 (P = 0.056) 90-day mortality: TM: 19% SC: 13% (P = 0.248) 90-day mortality in patients treated with tPA: 19%	Mean NIHSS at discharge: TM: 6.0 (SD 7.3) SC: 6.8 (SD 7.9) (P = 0.50) % 90-day mRS (dichotomized):[h] TM: 47% SC: 43% (P=0.69)	In-hospital complications: TM: 23% SC: 22% (P=0.85) In-hospital hemorrhage: TM: 7.6% SC: 6.4%	Complete data available for 30 (64%) patients in TM group and 188 (72%) in SC.
Sairanen et al. 2011[13] TM vs. SC outcomes	Onset to tPA (TM only): 120	NR	In-hospital mortality: TM tPA: 10%	% patients with 90 day mRS 0-1: TM tPA: 29%	ICH: TM tPA: 6.7% SC tPA: 9.4%	In some cases of data collection – data may not have

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Mean pre-treatment NIHSS: TM tPA: 10 (3 – 26) TM no tPA: 2.5 (0 – 25) (P < 0.0004) SC tPA: 10			no tPA: NR SC tPA: NR 90 day: TM tPA: 11.5% SC tPA: 10.2% (P = 0.662)	SC tPA: 38% (P = 0.289)		been recorded after contraindications for thrombolysis were clear after the TM consultation. May have skewed data.
Zaidi et al, 2011[14] TM vs. SC Median pre-treatment NIHSS: TM: 12 (4–33) SC: 10.5 (2–38) (P = 0.5)	Onset to tPA: TM: 145.5 (SD 42.8) SC: 156.7 (31.6) (P = 0.09) Arrival to tPA: TM: 89.9 (SD 36.3) SC: 67.8 (SC 26.1) (P<0.01)	NR	90-day mortality: TM: 31.6 % SC: 30.4% (P = 0.6)	% patients with 90-day mRS ≤1: TM: 34.9% SC: 22.0% (P = 0.09) % patients with 90-day mRS ≤2: TM: 42.1% SC: 37.5% (P = 0.07)	90-day symptomatic ICH: TM: 1.2% SC: 5.1% (P = 0.1) 90-day asymptomatic ICH: TM: 16.2% SC: 18.6% (P = 0.7)	NR
Khan et al., 2010[15] TM & TC Mean pre-treatment NIHSS: TM: 16 (range 3-37) TC: 19 (range 6 -22) (P = 0.4)	Onset to door: TM: 92 min (range 18-210) TC: 102 min (range 24-171) (P = 0.68) Door to tPA treatment: TM: 82 (range 40	All patients analysed were treated with tPA	90-day mortality: 22.5% 7-day mortality: 9%	(available for 40 of 44 participants) % patients with mRS<2 after 90 days: 40% % patients with mRS = 2 after 90 days: 25%	NR	Comparable to other telestroke programs.

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	– 195) TC: 77 (range 27 – 146) (P = 0.46) Onset to tPA: TM: 171 (range 88 – 330) TC: 179 (range 115 – 260) (P = 0.76)			No differences between TM and TC treated patients (P = 0.689)		
Muengtaweepongsa et al., 2010[16] TM Mean pre tPA NIHSS: 15 (3 – 34)	Onset to treatment: tPA: 160 Door to tPA: 54	NR	90 day: tPA: 14%	% patients with 90 day mRS 0-1: 42%	Symptomatic ICH: 2% Asymptomatic ICH: 13%	Data for tPA-treated patients only.
Pervez et al., 2010[17] Median pre-treatment NIHSS: TM: 12 SC: 13 (P = 0.39)	Onset to tPA (median): TM: 130 SC: 140 (P = 0.06)	NR	In-hospital: TM: 17.4% SC: 14.9% (P = 0.57)	Ambulatory at discharge: TM: 77.7% SC: 73.8% (P = 0.5) % patients with post-treatment mRS 0-1 in overall study population (unclear as to time period): 34.8%	Symptomatic ICH <36 hours: TM: 5.2% SC: 3.9% (P = 0.58)	Discharge to home: TM: 30.5% SC: 28.6% (P = 0.74)
Audebert et al.,	NR	NR	90 day:	Institutional care at	NR	Decreasing

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2009[18] TM vs no TM Median NIHSS: TM: 5 no-TM: 6			TM: 16.8% no-TM: 15.1% (adjusted OR 0.93, 95% CI 0.74–1.17) 12 month: TM: 24.5% no-TM: 22.7% (adjusted OR 0.98; 95% CI 0.80–1.19) 30 month: TM: 34.5% no-TM: 32.0% (adjusted OR 0.95, 95% CI 0.79–1.14)	12 months: TM: 9.4% no-TM: 11.4% Home with severe disability at 12 months: TM: 13.9% no-TM: 19.4% Home with no severe disability[i] at 12 months: TM: 53.8% no-TM: 44.5% Institutional care at 30 months: TM: 8.7% no-TM: 10.1% Home with severe disability at 30 months: TM: 11.2% no-TM: 13.2% Home with no severe disability: TM: 46.8% no-TM: 41.6%		differences over time may be due to increasing impact of age or other disease.

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Pedragosa et al., 2009[19] pre-TM vs. post-TM in patients receiving tPA therapy Median pre-treatment NIHSS scores: pre-TM: 19 (17-20) post-TM: 18 (11-19) (P = 0.31)	Onset to treatment: pre-TM: 210 (SD 43) post-TM: 162 (SD 84) (P = 0.05)	Unnecessary transfers to urban stroke centre: pre-TM: 51% post-TM: 20% (P = 0.02)	NR	Discharge NIHSS in patients receiving tPA: pre-TM: 5 (1–15) pot-TM: 4 (1–17) (P = 0.96)	NR	Treated within 3 hours: pre-TM: 30% post-TM: 68% (P = 0.04) Treated at the community hospital: pre-TM: 0% post-TM: 63% (P = 0.001) Received thrombolytic treatment: pre-TM: 4.5% post-TM: 9.6% (P = 0.07) Community hospital physicians found the telestroke service helpful, thought it was beneficial to patients.
Switzer et al., 2009[20] TM vs academic ED	Onset to treatment: TM: 127.6 (SD 36,	NR	In-hospital mortality: TM: 6%	NIHSS 24 hours after treatment: 8.3 (median 6)	Symptomatic ICH: TM: 2% ED: 0%	44% TM patients discharged to home, 34% to

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Mean pre-treatment NIHSS: 14.4 (median 12)	95% CI 117.1 – 138.0) ED: 145.9 (SD 47, 95% CI 126.9 – 164.9) (P = 0.0651) Treatment within 2h of symptom onset: TM: 50% ED: 35% Treatment within 90 min of symptom onset: TM: 22% ED: 19%				(P = 1.0)	inpatient rehabilitation, 10% to nursing home

BI = Barthel Index; CI = confidence interval; ED = emergency department; LSP = local stroke physician; min = minutes; mRS = modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale; NR = not reported; NS = not significant; OR = odds ratio; RCT = randomized controlled trial; TC = teleconsultation; TM = telemedicine; tPA = tissue plasminogen activator; SC = stroke centre

[a]: No technical problems influenced the outcome of the treatment decision, however, some did influence the amount of time the consultation took.
[b]: NIHSS score in the patients who received tPA treatment in the telemedicine group was 16
[c]: data available for 80 patients in the LSP group and 88 patient in the TC group
[d]: indicates moderately severe or severe disability
[e]: data available for 54 patients in the LSP group, 59 patients in the TC group
[f]: data available for 44 patients in the TM group and 280 in the SC group
[g]: data available for 42 patients in the TM group and 277 in the SC group
[h]: data available for 30 patients in the TM group and 179 in the SC group
[i]: severe disability defined as modified Rankin scale score >3 or Barthel index score <60
[j]: data missing for 21 TC patients