

# Efficacy of site-independent telemedicine in the STROKE DOC trial: a randomised, blinded, prospective study



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## Summary

**Background** To increase the effective use of thrombolytics for acute stroke, the expertise of vascular neurologists must be disseminated more widely. We prospectively assessed whether telemedicine (real-time, two-way audio and video, and digital imaging and communications in medicine [DICOM] interpretation) or telephone was superior for decision making in acute telemedicine consultations.

**Methods** From January, 2004, to August, 2007, patients older than 18 years who presented with acute stroke symptoms at one of four remote spoke sites were randomly assigned, through a web-based, permuted blocks system, to telemedicine or telephone consultation to assess their suitability for treatment with thrombolytics, on the basis of standard criteria. The primary outcome measure was whether the decision to give thrombolytic treatment was correct, as determined by central adjudication. Secondary outcomes were the rate of thrombolytic use, 90-day functional outcomes (Barthel index [BI] and modified Rankin scale [mRS]), the incidence of intracerebral haemorrhages, and technical observations. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00283868.

**Findings** 234 patients were assessed prospectively. 111 patients were randomised to telemedicine, and 111 patients were randomised to telephone consultation; 207 completed the study. Mean National Institutes of Health stroke scale score at presentation was 9.5 (SD 8.1) points (11.4 [8.7] points in the telemedicine group versus 7.7 [7.0] points in the telephone group;  $p=0.002$ ). One telemedicine consultation was aborted for technical reasons, although it was included in the analyses. Correct treatment decisions were made more often in the telemedicine group than in the telephone group (108 [98%] vs 91 [82%], odds ratio [OR] 10.9, 95% CI 2.7–44.6;  $p=0.0009$ ). Intravenous thrombolytics were used at an overall rate of 25% (31 [28%] telemedicine vs 25 [23%] telephone, 1.3, 0.7–2.5;  $p=0.43$ ). 90-day functional outcomes were not different for BI (95–100) (0.6, 0.4–1.1;  $p=0.13$ ) or for mRS score (0.6, 0.3–1.1;  $p=0.09$ ). There was no difference in mortality (1.6, 0.8–3.4;  $p=0.27$ ) or rates of intracerebral haemorrhage after treatment with thrombolytics (2 [7%] telemedicine vs 2 [8%] telephone, 0.8, 0.1–6.3;  $p=1.0$ ). However, there were more incomplete data in the telephone group than in the telemedicine group (12% vs 3%, 0.2, 0.1–0.3;  $p=0.0001$ ).

**Interpretation** The authors of this trial report that stroke telemedicine consultations result in more accurate decision making compared with telephone consultations and can serve as a model for the effectiveness of telemedicine in other medical specialties. The more appropriate decisions, high rates of thrombolysis use, improved data collection, low rate of intracerebral haemorrhage, low technical complications, and favourable time requirements all support the efficacy of telemedicine for making treatment decisions, and might enable more practitioners to use this medium in daily stroke care.

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## Introduction

Few patients with stroke (2–3%) receive thrombolytics, although the therapy has been approved for more than 10 years.<sup>1</sup> Thrombolytic therapy must be used rapidly and appropriately if stroke disability is to be reduced.<sup>2</sup> Previous approaches to increase the rates of treatment have failed, partially because of incomplete dissemination of stroke expertise regarding thrombolytic use and geographical restrictions. Greater availability of stroke specialists should increase the use of appropriate treatments and minimise protocol violations.<sup>3,4</sup> Telemedicine, which has already been implemented in many specialties, could enable the dissemination of stroke expertise for consultation, education, and research.<sup>5–8</sup>

Telemedicine is a reliable way to measure deficits due to stroke.<sup>9–12</sup> Remote assistance by telephone<sup>13</sup> or telemedicine

increases the use of thrombolytics,<sup>14–16</sup> but although many telemedicine systems are available, few randomised trials have been done,<sup>17</sup> and the efficacy of decision making is unknown. To assess the correctness of decision making in the time-pressured setting of acute stroke, we compared telemedicine (remote audio or video and radiological review) with telephone consultations, to test the hypothesis that telemedicine increases the efficacy of decision making. If telemedicine decisions are appropriate, this technology can be immediately implemented in daily practice.

## Methods

### Patients

Between January, 2004, and August, 2007, 234 patients were enrolled and 222 were randomly assigned to telemedicine or telephone-only consultations when they

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presented with symptoms of acute stroke at one of four remote sites (spokes) that were located 30 to 350 miles from an academic hub. 11 run-in patients were not randomised. Inclusion criteria were age at least 18 years,

ability to sign consent (or have a surrogate sign for them), and symptoms of acute stroke. There were no specific exclusion criteria. Written, informed consent was obtained at the spoke and sent to the hub consultant by internet fax before randomisation.

The trial was approved by the Human Research Protections Programs at the hub centre and the spoke facilities and was registered at ClinicalTrials.gov, number NCT00283868.

**Procedures**

The hub stroke team was contacted by pager system when a patient presented at the spoke. Patients were randomised with permuted blocks that were stratified by study site to prevent group imbalances. The randomisation to telemedicine or telephone-only consultation was done in real-time with a web-based randomisation system, which eliminated practitioner preference bias. For patients who were randomised to telemedicine, the consultation started with site-independent access to the telemedicine system. The hub consultant turned on the camera and immediately took a medical history and did an examination with the National Institutes of Health stroke scale (NIHSS). Other elements of the examination were done by, or reported to, the consultant as appropriate. Head CT images were viewed with a digital imaging and communications in medicine (DICOM) viewer. For patients who were randomised to telephone consultation, the hub consultant queried the spoke practitioner about history, physical assessment, the results of laboratory tests, and the local radiologist's report of the CT, and directed the local practitioner in the NIHSS examination. Neither the video nor the head CT images were viewed by the consultant.

In both groups, the consultant completed a prespecified case report form. The consultant was free to repeat examination items and could speak to available family members or witnesses. Clinical deficit and functional scale scores (including the NIHSS and prestroke and post-stroke modified Rankin scale [mRS] score) were calculated by the consultant with the information supplied by the bedside practitioner. After review of the history, the findings on examination, stroke and outcome scales, and interpretation of the head CT, the hub consultant gave a recommendation for thrombolytic treatment to the spoke emergency department practitioner.

The main objective of the trial was to establish the efficacy of telemedicine consultations for decision making. The primary outcome measure was whether the decision to give thrombolytics was appropriate, as established with a rigorous, multistage, masked adjudication process, the details of which have been published.<sup>18</sup> Secondary outcomes were rates of thrombolytic use, 90-day outcomes, rates of intracerebral haemorrhage, the completeness of the data, and technical observations.

Equipment included internet-enabled laptops used by a pool of three fellowship-trained vascular neurologists

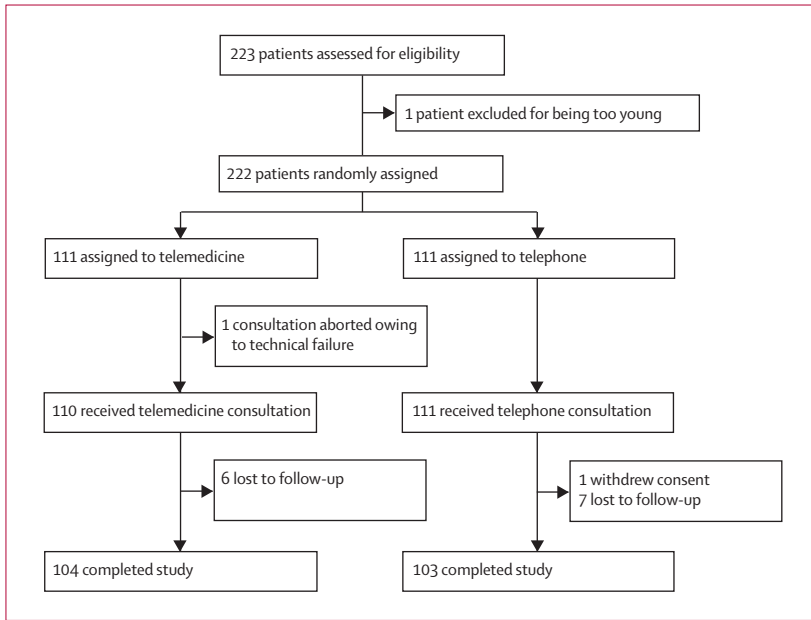


Figure 1: Trial profile

	Overall (n=222)	Telemedicine (n=111)	Telephone (n=111)	Estimate
Age (years)	69.7 (14.7)	70.4 (14.5)	69.0 (14.9)	1.40 (-2.5 to 5.3)*
Women	114 (51%)	57 (51%)	57 (51%)	1.00 (0.59 to 1.69) †
Ethnic origin				
White	211 (95%)	106 (96)	105 (95%)	
Black	6 (3%)	4 (4%)	2 (2%)	
Pacific islander	4 (2%)	1 (1%)	3 (3%)	
Asian	1 (1%)	0 (0%)	1 (1%)	
Not hispanic	120 (54%)	60 (54%)	60 (54%)	1.00 (0.59-1.69) †
Weight (kg)	80.0 (20.5)	79.7 (18.8)	80.5 (36.7)	-0.8 (-7.1 to 5.5)*
Risk factors				
CAD	61 (28%) [6%]	37 (33%) [3%]	24 (22%) [10%]	
Myocardial infarction	17 (8%) [14%]	12 (11%) [12%]	5 (5%) [15%]	
History of CVA	81 (37%) [5%]	40 (36%) [5%]	41 (37%) [5%]	
Atrial fibrillation	29 (13%) [7%]	19 (17%) [5%]	10 (9%) [8%]	
Diabetes	78 (35%) [4%]	43 (39%) [2%]	35 (32%) [5%]	
Hypertension	164 (74%) [3%]	83 (75%) [5%]	81 (73%) [5%]	
Hyperlipidaemia	75 (34%) [15%]	45 (41%) [7%]	30 (27%) [23%]	
Family history of stroke or TIA	23 (10%) [28%]	18 (16%) [18%]	5 (5%) [39%]	
Current alcohol use	30 (14%) [22%]	15 (14%) [9%]	15 (14%) [34%]	
Current tobacco use	21 (10%) [20%]	13 (12%) [9%]	8 (7%) [31%]	

CAD=coronary artery disease. CVA=cardiovascular attack. TIA=transient ischaemic attack. Data are mean (SD). \*Odds ratio (95% CI). †Difference in means (95% CI), number (percentage) [percentage unknown]. Unknown percentages are included because they might drive the significance of the comparison.

Table 1: Demographics and risk factors of patients

and the telemedicine systems at remote emergency departments. The software enabled site-independent access to two-way audio and high-resolution video, over standard internet connection (BF Technologies, San Diego, CA, USA).

The STRoKE DOC (Stroke Team Remote Evaluation using a Digital Observation Camera) adjudicating committee (SDAC) comprised specialist physicians who were trained in acute stroke management, and excluded practitioners from the remote spoke facilities. Level 1 adjudication included the hub consultant's review of the case, with the SDAC masked to consultation technique. For level 2a adjudication, an independent monitor reviewed the emergency department and admission record of the spoke and adjudicated on the correctness of the decision to give thrombolytics on the basis of the NINDS inclusion or exclusion criteria.<sup>3,4</sup> On the basis of detailed discussions, and still masked to the group assignment, the SDAC gave a separate level 2b assessment as to whether the decision was appropriate after taking in to account all information that would have been available at bedside. The level 2b decision was the primary outcome measurement. Detailed protocols were followed to ensure that the SDAC members remained blinded to each arm.<sup>18</sup> The consultant and monitor were not present during voting.

### Statistical analysis

A  $\chi^2$  test (2-sided,  $\alpha=0.05$ ) was used to estimate the power of the study as 80%, which assumed a correct decision rate with telephone-only of 80%, a telemedicine effect size of 10%, and sample size of 400. Statistical analysis for the primary outcome was done with a random-effects logistic regression model.<sup>19</sup> The effect of the adjudication decision was modelled as a function of the treatment arm. Site was included in the model as a random effect with an exchangeable correlation structure. Owing to sparse arrays, the Cochran-Mantel-Haenszel (CMH)  $\chi^2$  test, stratified by site, and fixed-effect logistic regression were done as sensitivity analyses. The Cochran-Mantel-Haenszel  $\chi^2$  test, stratified by site, and fixed-effect logistic regression were used for all other correct decision outcomes. Fisher's exact test was used for the rate of thrombolytic use, the rate of intracerebral haemorrhage, mortality, 90-day mRS score, and analysis of missing data. The Wilcoxon rank sum test was used for 90-day Barthel index (BI) and time-point comparisons.

Data for three NIHSS items were incomplete, most commonly in the telephone group. To more accurately compare severity, the NIHSS score was adjusted by removing the three items that were found to be most frequently incomplete from the NIHSS scores of both groups. A random-effect, logistic-regression model, with a random effect for participant, was used to test for incomplete demographic or NIHSS data fields. All analyses were done with the statistical software R 2.1.1.

The trial was not restricted to a 3 h window, to replicate true acute stroke settings, in which time of onset is initially unknown. The investigators did not want to delay evaluations or exclude potential patients by mandating that it should be conclusively known that less than 3 h had passed since time of onset before starting a consultation. However, patients were enrolled for whom treatment disagreements were impossible (eg, patients who presented late [ $>3$  h after stroke onset]), thus artificially enhancing agreement in both arms. After about 200 patients were enrolled, the steering committee proposed that the trial might be underpowered because of this and recommended a conditional probability analysis for futility or efficacy. The steering committee was masked to the results when they made this recommendation. An analysis plan and a priori guidelines for possible trial termination were finalised before the statistical core did the analyses. The steering committee halted the trial after the blinded conditional power analysis showed probabilities ranging from 0.96 to 0.99 that one group would be superior to the other for the

For more on the statistical software see <http://www.R-project.org>

	Overall (n=222)	Telemedicine (n=111)	Telephone (n=111)	Estimate
Pre-stroke mRS (complete scale)				
Dichotomised (0–1)	164 (75%)	78 (72%)	86 (78%)	0.73 (0.40 to 1.35)*
0=no symptoms	141 (64%)	65 (60%)	76 (89%)	
1=no significant disability	23 (11%)	13 (12%)	10 (9%)	
2=slight disability	12 (6%)	8 (7%)	4 (4%)	
3=moderate disability	27 (12%)	15 (14%)	12 (11%)	
4=moderate-to-severe disability	16 (7%)	8 (7%)	8 (7%)	
5=severe disability	1 (1%)	0 (0%)	1 (1%)	
Baseline mRS (complete scale)				
Dichotomised (0–1)	39 (18%)	14 (13%)	25 (23%)	0.51 (0.25 to 1.04)*
0=no symptoms	12 (16%)	6 (6%)	6 (5%)	
1=no significant disability	27 (12%)	8 (7%)	19 (17%)	
2=slight disability	26 (12%)	15 (14%)	11 (10%)	
3=moderate disability	34 (16%)	14 (13%)	20 (18%)	
4=moderate-to-severe disability	68 (31%)	35 (32%)	33 (30%)	
5=severe disability	53 (24%)	31 (28%)	22 (20%)	
NIHSS	9.5 (8.1) [7.0]	11.4 (8.7) [10.5]	7.7 (7.0) [5.0]	3.70 (1.61 to 5.79)†
mNIHSS	7.3 (6.8) [5.0]	8.8 (7.4) [8.0]	5.9 (5.9) [4.0]	2.90 (1.13 to 4.67)†
Baseline CT				
Scan normal	78 (36%)	29 (26%)	49 (45%)	0.44 (0.25 to 0.77)*
Primary ICH	17 (8%)	9 (8%)	8 (7%)	1.14 (0.42 to 3.06)*
CT contradiction to thrombolytics	29 (14%)	17 (16%)	12 (11%)	1.48 (0.67 to 3.27)*
Thrombolytics subset NIHSS	14.5 (7.2)	16.3 (7.4)	12.3 (6.3)	4.00 (0.22 to 7.78)†
Thrombolytics subset mNIHSS	11.4 (6.6)	12.7 (6.7)	9.8 (6.2)	2.90 (–0.59 to 6.39)†
Pre-stroke function from the investigators' estimate of mRS before stroke, and baseline post-stroke severity estimated from mRS, NIHSS, and mNIHSS. mRS=modified Rankin scale score. ICH=intracerebral haemorrhage. NIHSS=National Institutes of Health stroke scale score. mNIHSS=modified National Institutes of Health stroke scale score. Data are number (percentage). *Odds ratio (95% CI). †Difference in means (95% CI), mean (SD) [median].				

Table 2: Stroke severity at baseline

	Overall (min)	Telemedicine (min)	Telephone (min)	p
<b>Times from onset</b>				
Onset to door	159.5 (215.7) (n=147)	163.2 (195.7) (n=77)	155.5 (237.2) (n=70)	0.35
Onset to call	185.5 (225.9) (n=216)	192.9 (234.4) (n=108)	178.1 (217.8) (n=107)	0.44
Onset to ECG	218.9 (220.2) (n=117)	220.6 (212.5) (n=59)	217.1 (229.7) (n=58)	0.41
Onset to lab	238.6 (240.5) (n=111)	227.0 (194.9) (n=57)	250.9 (282.2) (n=54)	0.39
Onset to decision	244.2 (226.0) (n=216)	258.0 (229.9) (n=107)	230.6 (222.4) (n=109)	0.07
Onset to thrombolysis*	150.7 (35.8) (n=55)	157.2 (37.3) (n=30)	143.0 (33.1) (n=25)	0.14
<b>Times from door</b>				
Door to evaluation by clinician	7.6 (29.3) (n=124)	8.8 (36.5) (n=68)	6.2 (17.1) (n=56)	0.61
Door to call	35.6 (51.1) (n=146)	31.7 (42.7) (n=78)	40.0 (59.4) (n=68)	0.38
Door to consent	71.8 (51.7) (n=146)	69.3 (43.2) (n=79)	74.8 (60.3) (n=67)	0.53
Door to ECG	61.8 (46.7) (n=82)	68.5 (47.6) (n=46)	53.3 (44.6) (n=36)	0.06
Door to lab	70.8 (62.3) (n=82)	70.8 (48.9) (n=46)	70.7 (77.0) (n=36)	0.34
Door to neuroexamination	70.1 (34.5) (n=142)	75.2 (32.8) (n=75)	64.4 (35.7) (n=67)	0.03
Door to reading of CT	84.8 (59.8) (n=119)	84.3 (47.4) (n=69)	85.4 (74.1) (n=50)	0.67
Door to decision	97.8 (54.0) (n=146)	99.8 (43.5) (n=77)	95.5 (64.1) (n=69)	0.20
<b>Times from call</b>				
Call to consent	33.7 (26.4) (n=214)	33.6 (25.5) (n=109)	33.9 (27.4) (n=105)	0.89
Call to neuroexamination	36.7 (32.7) (n=216)	43.4 (29.6) (n=109)	30.0 (34.4) (n=107)	0.0005
Call to decision	60.0 (31.8) (n=216)	64.7 (29.1) (n=108)	55.2 (33.9) (n=108)	0.03
<b>Times from consent</b>				
Consent to neuroexamination	4.7 (19.7) (n=214)	10.9 (15.2) (n=108)	-1.6 (21.8) (n=106)	0.0001
Consent to decision	27.5 (21.2) (n=214)	32.0 (17.3) (n=107)	22.9 (23.6) (n=107)	0.0001
Consent to thrombolysis†	48.4 (19.6) (n=54)	51.2 (17.8) (n=30)	44.8 (21.4) (n=24)	0.16
Decision to thrombolysis‡	12.5 (9.6) (n=54)	10.0 (9.8) (n=30)	15.6 (8.5) (n=24)	0.02

Relevant stroke code timepoints. Data are mean (SD) (number of participants). ECG=electrocardiogram. \*One patient was excluded for missing data on bolus time. †Two patients were excluded for missing data on time of consent and bolus time. ‡Two patients were excluded: one for missing data on bolus time and one negative outlier.

**Table 3: Evaluation times**

primary outcome at the end of the study, based on the data collected so far across a spectrum of future alternatives.

### Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

### Results

234 patients with symptoms of acute stroke were assessed—eleven non-randomised participants were assessed during the run-in phase—and 222 patients were randomised (figure 1). There were no demographic differences between groups. 90-day outcomes were available for 218 (93%) patients. The risk factors coronary

artery disease ( $p=0.026$ ), hyperlipidaemia ( $p=0.003$ ), family history of stroke or transient ischaemic attack (TIA;  $p=0.0002$ ), current alcohol use ( $p<0.0001$ ), and current tobacco use ( $p=0.0004$ ) were greater in the telemedicine group (table 1).

Table 2 shows stroke severity at baseline. The mean NIHSS score was lower in the telephone group than in the telemedicine group ( $p=0.002$ ), and for the patients who were given thrombolytics ( $p=0.044$ ); patients in the telephone group had less severe strokes (mRS score=0 or 1) at baseline than did the telemedicine group but this difference did not reach statistical significance ( $p=0.077$ ). Furthermore, more baseline CT scans were normal in the telephone group than in the telemedicine group ( $p=0.0048$ ).

Table 3 shows the evaluation times for patients. Time from onset to door was 7.7 min shorter in the telephone group, although the difference was not significant ( $p=0.352$ ); and the time from onset to decision was shorter in the telephone group, although this was not significant ( $p=0.067$ ). The time from door to decision was not different between the groups (97.8 min); neither was the time from call to informed consent (33.7 min). The time from consent to decision (consultation duration) took 9.2 min longer for the telemedicine group ( $p<0.0001$ ). The time from consent to thrombolysis took 6.4 min longer in the telephone group, although the difference was not significant ( $p=0.163$ ). The time from decision to thrombolysis took 5.6 min longer in the telephone group ( $p=0.019$ ).

Correct treatment decisions were made more often with telemedicine than by telephone-only consultations, as shown by the primary outcome measure (level 2b adjudication) in table 4 (OR 10.9, 95% CI 2.7–44.6;  $p=0.0009$ ). The hub consultants also made correct decisions more frequently with telemedicine than by telephone only when assessed at level 1 (7.2, 2.1–24.6;  $p=0.0009$ ). There were no differences between the groups in the percentage of patients who reached 90-day BI (95–100), 90-day mRS scores (dichotomised 0–1), or mortality (table 4).

In the thrombolysis subgroup, the treatment decision was correct more often in the telemedicine group (30 [97%] vs 19 [76%], 7.4, 1.03–53.2;  $p=0.047$ ) than in the telephone group. There was a difference in the unadjusted mortality (39% telemedicine vs 12% telephone, 4.6, 1.1–19.0; unadjusted  $p=0.034$ ); however, after adjustment for the imbalanced NIHSS score at baseline, the difference was not significant ( $p=0.17$ ). There were no differences in post-thrombolytic intracerebral haemorrhage, decision to death time, percentage of deaths within 2 days, or death within 7 days for the overall trial or thrombolysis subgroup (table 5). There was no difference between the groups in the treatment of mild (mRS score 0–1) strokes with thrombolytics (0% telemedicine vs 4% telephone;  $p=0.45$ ).

All level 2b protocol violations are shown in table 6. The most common violations in the six patients in the telephone group who were treated with thrombolysis included treatment more than 3 h after onset of symptoms or treatment when they had rapidly improving or mild symptoms. The two violations in the patients in the telemedicine group that received thrombolytics were treatment of a patient who might have woken up with vertigo and treatment of a patient without excluding a potential aortic dissection. At 90 days, the six patients in the telephone group reached a mean BI score of 66, whereas the two patients in the telemedicine group reached a mean BI score of 100.

In 14 telephone consultations, the opinion of the adjudicating body was that thrombolytics should have been offered (table 6). Reasons included milder symptoms, less than 3 h since onset, isolated aphasia, mild CT changes, fluctuating symptoms, improving symptoms, and failure to try blood pressure control. At 90 days, 12 patients in the telephone group reached a mean BI score of 89, one patient died, and two patients had missing outcomes.

Reasons for appropriate non-treatment within 3 h included mild deficit (n=25), TIA or rapidly improving symptoms (n=21), haemorrhage on the initial CT (n=19), stroke mimic (n=13), seizure at onset (n=3), pronounced hypodensity on CT (n=2), and elevation of international normalised ratio treatment (n=2).

The demographics and NIHSS analysis combined showed a difference in the percentage of non-completed elements from the case report forms (3% telemedicine vs 12% telephone; OR 0.2, 95% CI 0.1–0.3; p<0.0001). There was a difference in the amount of missing data for five risk factors, which could influence patient outcome: coronary artery disease (3% telemedicine vs 10% telephone; p=0.05); hyperlipidaemia (7% vs 23%; p=0.002); family history of stroke or TIA (18% vs 39%; p=0.0001); alcohol use (9% vs 34%; p<0.0001); and tobacco use (9% vs 31%; p<0.0001).

For the NIHSS, there were differences in non-completed data for loss of consciousness questions (telemedicine 1% vs telephone 10%; p=0.005), loss of consciousness commands (1% vs 8%; p=0.019), gaze (1% vs 16%; p<0.0001), visual fields (1% vs 35%; p<0.0001), face (1% vs 8%; p=0.019), left leg (1% vs 7%; p=0.035), ataxia (1% vs 35%; p<0.0001), sensory (1% vs 15%; p<0.0001), dysarthria (1% vs 9%; p=0.010), and neglect (1% vs 40%; p<0.0001).

Site-independent evaluations were done in 110 (99%) telemedicine consultations. 15 consultations (14%) used wireless technology: 802.11 (14) and EVolution, Data-Optimized (EV-DO) broadband wireless (1). 99 (87%) used local area network (LAN) wired internet access.

Consultations were done evenly among sites, spoke emergency department practitioners, and consultants. 31 (14%) consultations were done at site one, 121 (55%) at site two, 19 (9%) at site three, and 51 (23%) at site four. 48 spoke emergency department practitioners

	Telemedicine‡ (n=110)	Telephone (n=111)	Odds ratio	p
<b>Primary outcome: overall correct decision</b>				
Level 2b (SDAC)	108 (98%)	91 (82%)	10.9 (2.7–44.6)	0.0009 (0.0001)
<b>Secondary outcomes: overall correct decision</b>				
Level 1 (SDAC)	107 (97%)	92 (83%)	7.2 (2.1–24.6)	0.0009
Level 2a (MM)	106 (96%)	103 (93%)	2.0 (0.6–6.9)	0.40
Level 3a (MM)	107 (97%)	103 (93%)	2.7 (0.7–10.5)	0.24
Level 3b (SDAC)	107 (97%)	92 (83%)	7.2 (2.1–24.6)	0.0008
Overall IV thrombolytic treatment	31 (28%)	25 (23%)	1.3 (0.7–2.5)	0.42
Overall post-consultation intracerebral haemorrhage	2 (7%)	2 (8%)	0.8 (0.1–6.3)	1.0†
90-day BI score (95–100)*	45 (43%)	56 (54%)	0.6 (0.4–1.1)	0.13†
90-day mRS score* (dichotomised 0–1)	36 (34%)	48 (47%)	0.6 (0.3–1.1)	0.09†
Overall mortality	21 (19%)	14 (13%)	1.6 (0.8–3.4)	0.27†

Primary and secondary analyses for each arm of the trial. Results are shown as overall for the trial. Many levels of adjudication were done, with the primary outcome being done at level 2b. Data are number (percentage), odds ratio (95% CI), p value calculated by random-effect logistic regression, clustered by sites (Cochran-Mantel-Haenszel  $\chi^2$  test) for the primary outcome and by Cochran-Mantel-Haenszel  $\chi^2$  test for secondary outcome. Fixed-effect logistic regression analysis gave similar results. SDAC=STRokE DOC adjudicating committee. MM=medical monitor. BI=Barthel index. mRS=modified Rankin scale. \*Total analysed in the telemedicine group=105; total analysed in the telephone group=103. †p values calculated with Fisher's exact test. ‡One patient did not complete the video consultation owing to a technical failure and could not be adjudicated.

**Table 4: Overall primary and secondary analyses**

	Telemedicine (n=31)	Telephone (n=25)	Odds ratio	p
<b>Thrombolysis subgroup: correct decision</b>				
Level 1 (SDAC)	30 (97%)	20 (80%)	13.7†	0.11
Level 2a (MM)	29 (94%)	19 (76%)	4.6 (0.9–25.0)	0.10
Level 2b (SDAC)	30 (97%)	19 (76%)	7.4 (1.0–53.2)	0.05
Level 3a (MM)	30 (97%)	21 (84%)	10.2†	0.12
Level 3b (SDAC)	30 (97%)	21 (84%)	10.2†	0.26
Post-thrombolytic intracerebral haemorrhage	2 (7%)	2 (8%)	0.8 (0.1–6.3)	1.0‡
90-day BI score (95–100)*	10 (33%)	12 (48%)	0.5 (0.2–1.6)	0.29‡
90-day mRS score (dichotomised 0–1)*	9 (30%)	8 (32%)	0.9 (0.3–2.9)	1.0‡
Subgroup mortality	12 (39%)	3 (12%)	4.6 (1.1–19.0)	0.03‡
Mortality adjusted for baseline NIHSS			3.4 (0.6–19)	0.17§

Primary and secondary analyses for each arm of the trial. Results are shown for thrombolysis group. Many levels of adjudication were done, with the primary outcome being done at level 2b. Data are number (percentage), odds ratio (95% CI), p value calculated by Cochran-Mantel-Haenszel  $\chi^2$  test. MM=medical monitor. BI=Barthel index. mRS=modified Rankin scale. \*Total analysed in the telemedicine group=30; total analysed in the telephone group=25. ‡CIs not included because of small sample size. †p values calculated with Fisher's exact test. §p value calculated with logistic regression.

**Table 5: Primary and secondary analyses for thrombolysis-only subgroup**

requested consultations: 18 (38%) practitioners initiated only one consultation, whereas 34 (71%) practitioners initiated between one and five consultations. Only five practitioners (10%) initiated more than ten consultations, and only one (2%) practitioner initiated more than 12. Remote consultant one did 93 (42%) consultations, consultant two did 67 (30%), and consultant three did 62 (28%).

	Group	Thrombolysis	Reason for disagreement	ICH	90-day outcomes
1	Telephone	N	Would have treated mild arm weakness and NIHSS=3	N	BI=100, mRS=0
2	Telephone	N	Patient did not wake with deficit, rather it was notice in the bathroom; probably in the 3-h window and would have treated	N	Death
3	Telephone	N	Would have treated mild deficit	N	BI=100, mRS=0
4	Telephone	Y	Decision made too quickly; blood pressure >185 mm Hg and would have rechecked because it was still within 3-h window	N	BI=75, mRS=4
5	Telephone	N	Would have treated predominant symptoms	N	BI=100, mRS=0
6	Telephone	N	Not a TIA; would have treated aphasia	N	BI=85, mRS=3
7	Telephone	N	Would have treated mild symptoms	N	Withdrew consent
8	Telephone	N	Would have treated patient with early hypodensity (probably early ischaemic changes only)	N	BI=80, mRS=3
9	Telephone	Y	Would not have treated; probably >3 h	N	BI=100, mRS=0
10	Telephone	N	Would have treated aphasia (patient was a teacher)	N	BI=100, mRS=0
11	Telephone	Y	Open wound; would have waited for blood glucose measurement	N	BI=10, mRS=5
12	Telephone	N	Fluctuating symptoms; would have waited longer	N	Lost to follow-up
13	Telephone	Y	Would not have treated; >3 h	N	BI=100, mRS=2
14	Telephone	N	No CT scan; would have treated mild deficit	N	BI=100, mRS=0
15	Telephone	N	Would have treated improving symptoms	N	BI=100, mRS=1
16	Telephone	N	Would have treated aphasia and weakness	N	BI=100, mRS=1
17	Telephone	N	No attempt to lower blood pressure, and patient had measurable deficit	N	BI=100, mRS=0
18	Telephone	Y	Mild isolated sensory deficit; would not have treated	N	BI=55, mRS=4
19	Telemedicine	Y	Possibility of aortic dissection not fully excluded	N	BI=100, mRS=0
20	Telemedicine	Y	Onset time questionable for posterior circulation stroke (patient woke with vertigo)	N	BI=100, mRS=2
21	Telephone	Y	Would not have treated owing to blood pressure exclusion	N	BI=75, mRS=4
22	Telephone	N	Would have treated aphasia, slurred speech, and sensory loss	N	BI=100, mRS=1

Reasons for adjudication disagreements at the primary (level 2b) adjudication level, including number of disagreements at that level. Y=yes. N=no. NIHSS=National Institutes of Health stroke scale score. ICH=intracerebral haemorrhage. BI=Barthel index. mRS=modified Rankin scale score.

**Table 6: Adjudication disagreements**

Technical observations were noted in 12 (19%) teleconsultations. Only one (1%) could not be done because of technical failure, but this case was included in the intention-to-treat analyses. Of the other 11 observations, six were due to problems with the radiological interface, three were audio difficulties, one was a camera control failure, and one was a delay in obtaining faxed consent.

There were no differences in diagnoses. Only 17 (8%) patients were discharged from the emergency department with a diagnosis of non-stroke or non-TIA. Although patients could be excluded for many reasons, the most common thrombolytic exclusions were more than 3 h since onset (43% telephone *vs* 60% telemedicine; unadjusted  $p=0.03$ ), mild or resolving symptoms (52% telephone *vs* 34% telemedicine; unadjusted  $p=0.02$ ), no measurable deficit (42% telephone *vs* 33% telemedicine;  $p=0.26$ ), and unknown onset (28% telephone *vs* 23% telemedicine;  $p=0.48$ ).

## Discussion

The results of this prospective, blinded, randomised trial show that telemedicine is efficacious for making acute medical decisions. Stroke telemedicine is widely implemented and discussed,<sup>8,14,18,20–23</sup> but despite its

dissemination, its efficacy has not previously been shown. Our results support the use of telemedicine to make urgent treatment decisions, such as whether to use thrombolytic therapy for acute stroke.

Current rates of thrombolytic use are low and could be increased,<sup>1,24,25</sup> our data show that this could be achieved by improving the availability of stroke specialists. Telephone assistance increases treatments<sup>13</sup> but, as we have shown, telemedicine is preferable because it improves the number of correct decisions. Clinicians in emergency departments who hesitate to give thrombolytics despite their willingness and ability to identify eligible patients might feel more comfortable with telemedicine back-up.<sup>26–28</sup>

Despite the high number of correct decisions made in this trial, 3-month functional outcomes (defined as the percentage of patients who have a BI score of 95–100 or dichotomised mRS score [0–1]) were not different between the groups. The high rate of treatment with thrombolytics in the telephone group might have been the reason for the absence of difference, and further analysis will show whether differences in post-stroke care affected the outcomes. Although this study was not powered to show improved functional outcomes, the

failure to show a functional benefit for telemedicine in this trial might have also been due to the small sample size (the trial was halted early) and to the more severe deficit in the telemedicine group at baseline.

In the telemedicine group, there might have been an increased ability to complete the NIHSS, particularly for subtle findings, which led to a difference in the unadjusted baseline NIHSS scores between the two groups. Incomplete data acquisition might have contributed to the lower NIHSS in the telephone group. The consultant was NIHSS certified and directed the NIHSS examination in both groups; however, the spoke practitioners might not have been NIHSS certified. These features support the use of telemedicine to obtain a more accurate NIHSS score but made direct comparisons of NIHSS scores in this trial complex. To correct more rigorously for imbalances in severity at baseline, we adjusted the NIHSS by excluding three frequently incomplete items from the total NIHSS scores of both groups. After adjustment for missing items, the telemedicine group still had a higher total score than did the telephone group. On the basis of the NIHSS score, the telemedicine group presented with more severe strokes. A similar result was noted for mRS score (0–1), which further supports the greater severity of stroke in the telemedicine group.

STRoKE DOC was designed to compare two consultation techniques, not to assess the efficacy of thrombolytics. The thrombolysis telemedicine subgroup had a high baseline NIHSS score (mean=16) and a high percentage of participants with coronary disease (26%), diabetes (32%), and hypertension (32%), which might have been integral to the patient outcome. The 90-day mortality in the thrombolysis telemedicine subgroup was higher than that in other reports of large-scale telemedicine, which showed good functional outcome and lower mortality.<sup>15,16</sup>

Owing to the small number of patients who were given thrombolytics in the telemedicine group, the results of the unadjusted subgroup mortality analyses should be viewed cautiously, and might have been due to chance. After correction for imbalances in the baseline NIHSS scores, the difference in mortality in the thrombolysis subgroup was not significant. The result also loses significance if adjusted for multiple comparisons. We were reassured that there was no difference in the rates of intracerebral haemorrhage or early death after thrombolytics, and 90-day functional outcomes were not different for the BI (95–100) or the mRS. The finding for the unadjusted subgroup is inconsistent with clinical reports: the unadjusted mortality for the patients in the telephone subgroup who received thrombolytics was lower than that for the patients who received thrombolytics in the NINDS trial,<sup>3</sup> and the unadjusted mortality in the patients in the telemedicine subgroup who received thrombolytics was higher than that reported in recent large studies of telemedicine,<sup>15,16</sup> which have shown lower mortality after telemedicine-guided thrombolytic therapy.

Direct comparisons should not be made between trials with different patient populations or different post-stroke care protocols. Instead, larger trials with more patients given thrombolytics after telemedicine consultations would more appropriately measure long-term mortality in patients with stroke who are assessed with telemedicine.

Although we did not specifically measure post-thrombolysis care, the rates of post-thrombolytic intracerebral haemorrhage were measured because they can be the consequence of insufficient post-thrombolytic management and were the biggest concern. The rate of intracerebral haemorrhage (7–8%) was similar in both arms of the trial and was consistent with the rate reported in previous studies,<sup>3,29</sup> which suggests that post-thrombolysis care was adequate and balanced.

Because the data on the telephone group were less complete, we did not adjust for the more severe risk factors or the increase in CT findings in the telemedicine group. The CT reports in the telephone group were based on the initial interpretation by the local radiologist that was given to the emergency department. In the telephone arm, no images were viewed by a consultant, and subtle abnormalities that were later noted in the radiologist's final dictation might have been excluded from this local report. The difference in the number of normal CT scans might also have been because of the more detailed initial read by the vascular neurologist in the telemedicine group. Therefore, we did not adjust for the increase in CT findings in the telemedicine group because they might be artefacts. A complete central review of all the images is underway.

We did not intervene in the post-thrombolysis or post-care plans of the remote hospitals; rather, we only assessed a single variable of the consultation technique. Investigators in other studies are assessing the combination of telemedicine and stroke units.<sup>30</sup> A higher percentage of telephone patients who were given thrombolytics were transferred to the hub (18 of 31 in the telemedicine group and 19 of 25 in the telephone group, OR 0.44, 95% CI 0.11–1.59;  $p=0.26$ ). Although not statistically significant, these data suggest the need for further studies.

The duration of the consultation was estimated from the recorded time intervals, with the time that the consultation began recorded as time of consent. In the telephone arm, the times to neurological examination seem shorter because the examination done by the physician in the emergency department was sometimes reported at the time of the telephone discussion, whereas in the telemedicine arm, the consultant personally completed a history before doing the examination.

Obtaining consent requires discussion and was essential in this trial.<sup>31</sup> After consent was given, telemedicine consultations took longer (10 min) than telephone consultations because the telemedicine practitioner took a history, did the examination, and

reviewed the images. The improved decision making in telemedicine might justify this time difference, although long-term trials of patient outcome would be needed for verification. The favourable time requirement for telemedicine consultations (32 min) is probably less than that of bedside consultations, and has the advantage of eliminating driving time for patients and practitioners.

Our results emphasise the need for efficient stroke-code policies and rapid treatment strategies. Stroke-code times were generally not different between groups. If the consultant was contacted immediately, without the need for consent, these times would be more consistent with US guidelines.<sup>32</sup> The shorter decision time to thrombolytic treatment (6 min less for telemedicine) suggests that telemedicine might help to quantitatively lessen neuronal loss.<sup>33</sup> This reduction in time might have resulted from the consistent presence and encouragement of the telemedicine practitioner during this period.

Telemedicine improves the ability of consultants to obtain information before making treatment decisions. Data completion for key risk factors and NIHSS items was greater in the telemedicine group than in the telephone group. Despite encouraging the spoke practitioner during telephone consultations to return to the bedside to reassess the history and examination elements, the NIHSS was still often incomplete. The NIHSS items that had more than 15% of the data missing in the telephone group are also items that were previously documented to show poor interobserver reliability (gaze, visual fields, ataxia, sensory, and neglect).<sup>10,34,35</sup> The extent to which incomplete data collection directly affects decision making is not known, although this could lead to errors.

Despite the complexity of the telemedicine system, technical problems did not affect the successful completion of the trial. The reliability of the site-independence and quality of service<sup>18</sup> technology is shown by the fact that only one consultation was not possible because of technical failure.

The limitations of the trial must be noted. We could not measure the increase in thrombolytic use because we did not collect data before the trial. However, during the year before the trial started, only one facility had neurological support in the emergency department, and treatment with thrombolytics was rare. Another limitation is that stroke codes might not have been activated on all patients with stroke who presented to the sites; therefore, the true denominator is unknown.

We compared the telemedicine arm with a telephone-only arm because many emergency department clinicians attempt telephone discussions with specialists when no neurological consultant is available. The comparison of telemedicine with no consultation would have been impractical and potentially unethical. The chosen design, however, underestimated the true benefit of telemedicine because it was not compared with a placebo. Similarly, the telephone arm does not truly replicate standard

curbside telephone practice because our consultants were meticulous in determining onset time (eg, they called witnesses), filling out detailed case report forms, and dictating recommendations into the documentation record at the spoke. These features, which are inherent in a clinical trial but are scarce in clinical practice, might have led to more complete consultations and fewer telephone disagreements. Real-world telephone practice would be less effective than our telephone arm.

We implemented trial procedures to reduce the chances of unblinding of the adjudication committee. These rules restricted voting if there was concern that any member of the SDAC had deduced the randomisation. The consultant was the only SDAC member who knew which randomisation arm a patient was in and was excluded from the adjudication room during voting to minimise the potential for unblinding. Data were locked, and team members were blinded until all adjudications were complete. Although personally viewing the CT images might partly explain the improved decision making, our opinion is that teleradiology is an integral component of telemedicine and we have, therefore, not separated the two.

We chose an intrahospital, randomisation design to limit the learning or Hawthorne effects to only one arm of the trial or to only one facility, which might not have been well matched to another. This trial assessed one variable—adding telemedicine to stroke evaluations—and no care protocols were changed, to avoid contentions that any benefit was because of other improvements in care. 48 spoke emergency department clinicians initiated consultations from four different spokes, with most of the practitioners involved in only one to five consultations. The many sites and the limited involvement of a single emergency department clinician minimised any substantial learning effect.

In summary, the STRoKE DOC study established the benefit of telemedicine over telephone, specifically for acute medical decision making. Because thrombolytics reduce stroke-related disability when given correctly,<sup>3,33,36</sup> increasing the rapid and appropriate use of thrombolytics will benefit public health. Telemedicine is a viable solution that can now be added to the stroke armamentarium, enabling more practitioners to treat strokes rapidly and effectively, irrespective of their location. However, replication of these results and long-term patient-outcome trials are still needed.

#### Contributors

BCM and PDL had the idea for and designed the study; they participated in the acquisition, analysis, and interpretation of the data, drafting and revision of the manuscript, and provided administrative, technical, and material support, and supervised the study. PDL obtained the funding. RR participated in the design of the study, the analysis and interpretation of the data, revision of the manuscript, and statistical analysis. TH participated in the acquisition, analysis, and interpretation of data, and in revision of the manuscript. RO participated in the acquisition of data, revision of the manuscript, and study supervision. JAZ had the idea for and designed the study, participated in the analysis and interpretation of data, revised the manuscript, gave administrative, technical, and

material support, and supervised the study. RR participated in the revision of the manuscript, and provided administrative, technical, and material support. RGT participated in the analysis and interpretation of the data, revision of the manuscript, statistical analysis, and supervision of the study. All authors have seen and approved the final version of the manuscript.

#### Conflicts of interest

We have no conflicts of interest.

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