PAPER

Visible infarction on computed tomography is an independent predictor of poor functional outcome after stroke, and not of haemorrhagic transformation

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Objectives: To examine a very large dataset to provide a robust answer to the question of whether visible infarction on computed tomography was (a) an independent predictor of functional outcome at all times up to 48 hours after stroke, and (b) independently associated with haemorrhagic transformation, with or without antithrombotic treatment.

Methods: The study assessed associations between visible infarction, time to randomisation, baseline neurological deficit, stroke syndrome, allocated aspirin or heparin treatment, recurrent haemorrhagic stroke, early death and six month functional outcome in the International Stroke Trial.

Results: Of 12 550 patients, 6267 (50%) had visible infarction up to 48 hours after stroke. The prevalence of visible infarction increased with increasing time from onset and extent of the stroke syndrome. Visible infarction was independently associated with increased death within 14 days (odds ratio (OR) 1.17, 95% CI 1.02 to 1.35), and of death or dependency at six months (OR 1.42, 95% CI 1.31 to 1.55), an absolute increase of 13%, or 130 per 1000 more dead or dependent patients with visible infarction than without it. There was no significant independent relation between visible infarction and fatal or non-fatal haemorrhagic transformation, or interaction between visible infarction and aspirin or heparin treatment allocation with six month functional outcome.

Conclusions: Visible infarction on computed tomography up to 48 hours after stroke is an independent adverse prognostic sign.

Brain imaging is an integral component of the assessment of patients with acute stroke.[1] The appearance of the brain on imaging like computed tomography (CT) may influence treatment decisions in ischaemic stroke,[1] so it is important to extract as much diagnostic and prognostic information as possible from imaging. Several studies[2–29] have examined whether the presence of a visible infarct on a CT scan was associated with a worse prognosis after stroke. However, some of these studies were small[2–5 8 9 15 16 18]; or did not take account of possible confounding variables like baseline stroke severity[8 10 12 14–16]; reported only short-term outcome[2 4–6]; only considered infarction visible within the first few hours after stroke[3 5 7–13 20–26]; or defined "clinical outcome" by various different and not directly comparable means (for example, in some studies a "good" outcome was defined as 0 to 1 on the modified Rankin scale,[26] and as 0 to 4 in others[7]). Not all studies found a relation between visible infarction and worse outcome after stroke,[3 14 24 26 28] one possible reason being poor observer reliability for detecting very subtle early infarct signs.[30–32]

CT is likely to remain the cornerstone of rapid stroke investigation. Thus it is important to determine as precisely as possible the relation between visible infarction, the clinical features of the stroke, and early and late outcome events. In addition, it is also important to determine whether the response to any particular acute ischaemic stroke treatment might differ in patients who already have a visible infarct, compared with those who do not, after correcting for all other potentially confounding factors. To provide a reliable answer, we investigated this problem using a very large dataset from the hyperacute and acute phases of stroke, taken from the International Stroke Trial (IST), which included 19 435 patients from 467 hospitals in 36 countries worldwide, and randomised patients to aspirin, heparin, both or neither up to 48 hours after ischaemic stroke.[33]

METHODS

The IST recruited patients between 1991 and 1996 and has been described in detail previously.[33] Briefly, patients with presumed acute ischaemic stroke were eligible up to 48 hours after stroke if the responsible clinician thought that there was no definite indication for, or contraindication to, aspirin or heparin treatment. A CT brain scan was to be performed before randomisation if at all possible. The time of CT was not recorded. To analyse the effect of time after stroke on visible infarction, we restricted the analysis to these patients with CT prior to randomisation and used time of randomisation as a surrogate time for CT. Although therefore, the CT could have been an hour or possibly more before randomisation, time of randomisation at least provided us with a maximum possible time of CT.

At randomisation, the age and sex of the patient, the severity of the neurological deficit (up to eight possible deficits), conscious level, the Oxfordshire Community Stroke Project Classification (OCSP) stroke type,[34] atrial fibrillation, blood pressure, the number of hours from stroke onset to randomisation, and the result of the CT scan were collected. The neurological deficits recorded were as follows (all coded as yes/no/unassessable): unilateral weakness (and/or sensory

Abbreviations: CT, computed tomography; IST, International Stroke Trial; OCSP, Oxford Community Stroke Project Classification; TSCS, total anterior circulation syndrome; PACS, partial anterior circulation syndrome; POCS, posterior anterior circulation syndrome; LACS lacunar anterior circulation syndrome

Table 1 Visible infarction as a predictor of outcome in the IST: baseline variables and proportions of patients affected

	Infarct visible	%	No infarct visible	%
Number	6267		6283	
Delay, hours from symptoms				
0–3	101	(2)	282	(4)
4–6	419	(7)	795	(13)
7–12	1051	(17)	1449	(23)
13–24	1864	(30)	1724	(27)
25–48	2832	(45)	2033	(32)
Sex				
Male	3299	(53)	3484	(55)
Female	2968	(47)	2799	(45)
Age (y)				
<75	3689	(59)	3871	(62)
75+	2578	(41)	2412	(38)
Stroke type				
TACS	1877	(30)	1218	(19)
PACS	2508	(40)	2454	(39)
POCS	681	(11)	889	(14)
LACS	1180	(19)	1705	(27)
Other	21	(0.3)	17	(0.3)
Deficit score*				
1	453	(7)	554	(9)
2	736	(12)	1013	(16)
3	1306	(21)	1698	(27)
4	1207	(19)	1232	(20)
5	995	(16)	774	(12)
6	885	(14)	625	(10)
7	685	(11)	387	(6)

*Number of neurological deficits, but with 0 recorded as 1 and 8 recorded as 7, and if a deficit could not be removed, the patient was assumed to have that deficit.

deficit) affecting face; unilateral weakness (and/or sensory deficit) affecting arm/hand; unilateral weakness (and/or sensory deficit) affecting leg/foot; dysphasia; homonymous hemianopia; visuospatial disorder; brain stem/cerebellar signs; and other deficit.

The doctor/radiologist in the randomising hospital read the CT scan, and specified whether or not any infarct, that could be responsible for the recent stroke symptoms, was present on the CT scan. The scans were not forwarded to the trial coordinating office and were not read centrally. However, any discrepancy between the reading of the pre-randomisation scan, and subsequent reading by the hospital radiologist or senior stroke physician was recorded on the 14 day form. This form also recorded fatal or non-fatal events within 14 days of randomisation (chiefly recurrent ischaemic or haemorrhagic stroke).

Final follow up (blinded to treatment allocation, baseline characteristics, and CT appearance) was obtained at six months to ascertain all deaths within six months and functional status on those alive at six months. We classified functional outcome as poor if, at six months, they were dead from any cause, or were alive but needed help for everyday activities (Rankin Score 3 to 6).[33]

Patients with a final diagnosis of ischaemic stroke, and who had had a pre-randomisation CT scan were then identified from the trial database for the present analyses. Simple descriptive statistics were performed initially to examine the proportion of patients with a visible infarct within predefined time intervals after randomisation (0 to 3, 4 to 6, 7 to 12, 13 to 24, and 25 to 48 hours), by age (under 75 years, or 75 years or older), by OCSP stroke type, and by neurological deficit score. The neurological deficit was collapsed to give a deficit score, which was the sum of the eight possible deficits on presentation.[35]

Univariate analyses were performed to determine the association between visible infarction and deaths within 14 days of stroke, fatal or non-fatal recurrent ischaemic stroke, fatal or non-fatal recurrent haemorrhagic stroke, and death or dependency at six months.

Multivariate analyses were then performed adding clinical variables known to be predictors of poor stroke outcome, and visible infarction. Finally, further multivariate analysis were done to take account of time from stroke to randomisation, and for any interaction between visible infarction and the effect of aspirin or heparin treatment allocation on clinical outcome.

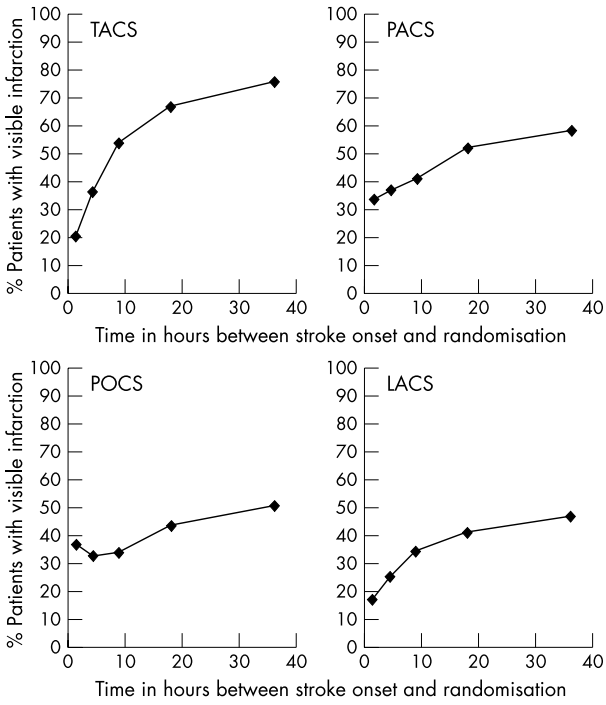

Figure 1 Proportion of patients with infarction visible on pre-randomisation CT by stroke subtype and time from onset to randomisation (note: time from onset to CT was not recorded, so this lapse is the longest time; delay to CT will have been shorter).

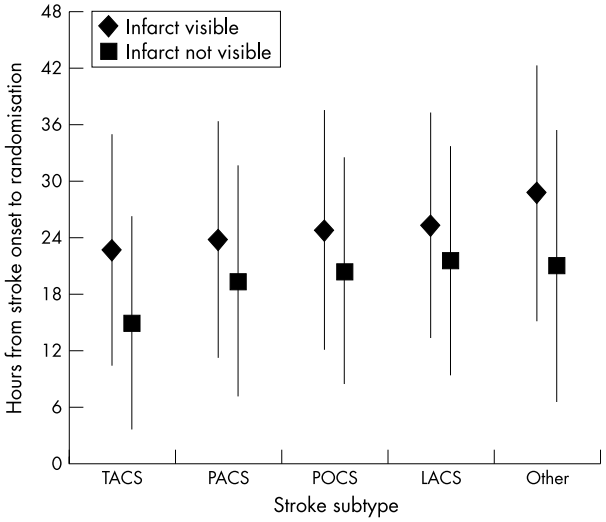

Figure 2 Mean (SD) time to randomisation of patients with and without a visible infarct by OCSP subtype.[34]

RESULTS

Of 19 435 patients randomised, 12 550 patients had a CT scan before randomisation and a final diagnosis of ischaemic stroke (including 1597 within six hours of stroke) and were included in the present analysis (table 1).[33] Of these 12 550 patients, the number and proportion with each of the OCSP infarct subtypes were: 3095 (25%) total anterior circulation syndrome (TACS); 4962 (40%) partial anterior circulation syndrome (PACS); 1570 (13%) posterior circulation syndrome (POCS); and 2885 (23%) lacunar syndrome (LACS).[34] Some 4990 (40%) patients were aged 75 years or older. There were 6783 men (54%).

Within the first 14 days after stroke 1193 patients (9.5%) had died, 449 patients (3.6%) had had a recurrent fatal or non-fatal ischaemic stroke, and 96 patients (0.8%) had had a recurrent fatal or non-fatal haemorrhagic stroke. At six months after stroke 7485 patients (60%) were dead or dependent.

The proportion of patients with infarction visible on their pre-randomisation CT scan increased with increasing time from onset (table 1 and fig 1) from 26% of those randomised within three hours, to 58% of those randomised between 25 and 48 hours after stroke. On subdividing by stroke syndrome, the highest proportion of patients with a visible infarct was in the group with a TACS, followed by the PACS, POCS, and LACS groups respectively (fig 1).

Patients with a visible infarct were on average randomised later than those without a visible infarct (fig 2). The mean time to randomisation after a TACS with a visible infarct was 22.8 hours (SD 12.2) compared with 15.0 hours (SD 11.3) without a visible infarct. The corresponding times in hours (SD) for the other stroke syndromes were: PACS 23.8 (12.5) with, 19.5 (12.2) without; LACS 25.4 (11.9) with, 21.6 (12.1) without; POCS 24.9 (12.7) with, 20.5 (12.0) without.

On univariate analysis (table 2), the presence of visible infarction was associated with an increased odds of being dead at 14 days (odds ratio (OR) 1.59, 95% confidence intervals (CI) 1.41 to 1.79), and dead or dependent at six months (OR 1.75, 95% CI 1.63 to 1.88). There was no strong evidence of a univariate association between visible infarction and recurrent fatal or non-fatal ischaemic stroke (OR 1.17, 95% CI 0.97 to 1.41) or recurrent fatal or non-fatal haemorrhagic stroke (OR 0.78 95% CI 0.52 to 1.17).

On subgroup analysis by stroke syndrome, the presence of a visible infarct was associated with an increased odds of being dead at 14 days, significantly in the patients with a PACS and POCS (OR 1.41, 95% CI 1.15 to 1.73, and OR 1.56, 95% CI 1.11 to 2.18 respectively), and there was a non-significant trend to increased early deaths in the TACS and LACS (OR 1.18, 95% CI 0.98 to 1.43, and 1.71, 95% CI 0.98 to 3.00 respectively). Visible infarction was also associated with an increased odds of being dead or dependent at six months, significantly for all stroke syndromes (TACS OR 1.29, 95% CI 1.06 to 1.58; PACS OR 1.57, 95% CI 1.40 to 1.76; LACS OR 1.51, 95% CI 1.30 to 1.75; and POCS OR 1.61, 95% CI 1.31 to 1.96).

On initial multivariate analyses, the factors identified as being significant predictors for death at 14 days and for death or dependency at six months in the logistic regression model are shown in table 3 (note that time from stroke to scan was not included at this stage). Visible infarction did not increase the odds of death within 14 days significantly (OR 1.10, 95% CI 0.96 to 1.25), but did significantly increase the odds of death or dependency at six months (OR 1.44, 95% CI 1.32 to 1.57). Visible infarction was not a significant predictor of recurrent fatal or non-fatal ischaemic stroke within 14 days (OR 1.12, 95% CI 0.92 to 1.36), though did appear to be associated with a reduction in the odds of recurrent fatal or non-fatal haemorrhagic stroke within 14 days (OR 0.64, 95% CI 0.42 to 0.98). However, there were only 96 fatal or non-fatal haemorrhagic strokes in the entire 12 550 subjects, and therefore this analysis should be regarded with caution.

The preceding analysis took account of stroke syndrome and severity, but it did not take account of time from stroke to randomisation, and that the patients with a visible infarction were seen later than those with no visible infarction (see above). In other words, it was possible that the apparent association between visible infarction and poor outcome was actually attributable to the patients arriving at hospital, and therefore reaching medical attention and treatment, later. We therefore added time to randomisation to the logistic regression model (table 4). Visible infarction was still an independent predictor of death at 14 days (OR 1.17 95% CI 1.02 to 1.35) and death or dependency at six months (OR 1.42, 95% CI 1.31 to 1.55). Visible infarction was not a significant predictor of recurrent fatal or non fatal ischaemic stroke within 14 days, or of fatal or non-fatal haemorrhagic stroke within 14 days (OR 0.79, 95% CI 0.51 to 1.21). Thus after also adjusting for the effect of time to randomisation visible infarction still remained an independent predictor of poor outcome.

We then examined whether there was any evidence that visible infarction changed the response to aspirin or heparin by repeating the logistic regression analysis including a term

Table 2 Visible infarction as a predictor of outcome in the IST: univariate analyses

	Infarct visible		No infarct visible	
End points/outcomes	n=6267	(%)	n=6283	(%)
Death within 14 days	719	(11)	474	(8)
Fatal or non-fatal recurrent ischaemic stroke within 14 days	241	(4)	208	(3)
Fatal or non-fatal haemorrhagic stroke within 14 days	42	(0.7)	54	(0.9)
Death or dependency at six months	4156	(66)	3329	(53)

Table 3 Visible infarction as a predictor of outcome in the IST: logistic regression model. (A) Death at 14 days, (B) death or dependency at six months

Variable	Odds ratio	95% Confidence intervals
(A) Death at 14 days		
Increasing age	1.32	1.22 to 1.43
Male	1.15	1.01 to 1.32
Not alert	3.68	3.14 to 4.30
Increasing deficit score	1.40	1.32 to 1.48
OTHER *v* TACS	1.81	0.24 to 13.60
LACS *v* TACS	0.64	0.45 to 0.91
PACS *v* TACS	1.04	0.88 to 1.23
POCS *v* TACS	1.28	1.03 to 1.60
Atrial fibrillation	1.45	1.24 to 1.69
Infarct visible	1.10	0.96 to 1.25
(B) Death or dependency at six months		
Increasing age	1.76	1.68 to 1.84
Male	0.76	0.70 to 0.83
Not alert	3.00	2.63 to 3.42
Increasing deficit score	1.53	1.47 to 1.59
OTHER *v* TACS	1.10	0.50 to 2.43
LACS *v* TACS	0.95	0.80 to 1.13
PACS *v* TACS	0.86	0.74 to 1.00
POCS *v* TACS	0.64	0.53 to 0.76
Atrial fibrillation	1.37	1.20 to 1.56
Infarct visible	1.44	1.32 to 1.57

Deficit score, sum of eight possible neurological deficits on presentation, with 0 recorded as 1 and 8 as 7. Age is standardised. A total of 493 patients with not known atrial fibrillation were removed from this analysis.

Table 4 Visible infarction as a predictor of outcome: logistic regression model including the effect of time to randomisation. (A) Death at 14 days, (B) death or dependency at six months

Variable	Odds ratio	95% Confidence intervals
(A) Death at 14 days		
Increasing age	1.33	1.23 to 1.44
Male	1.15	1.01 to 1.32
Not alert	3.60	3.08 to 4.22
Increasing deficit score	1.39	1.32 to 1.48
Increasing time to randomisation	0.99	0.98 to 1.00
OTHER *v* TACS	1.85	0.25 to 14.00
LACS *v* TACS	0.65	0.46 to 0.93
PACS *v* TACS	1.05	0.89 to 1.24
POCS *v* TACS	1.31	1.05 to 1.63
Atrial fibrillation	1.44	1.23 to 1.68
Infarct visible	1.17	1.02 to 1.35
(B) Death or dependency at six months		
Increasing age	1.75	1.67 to 1.84
Male	0.76	0.70 to 0.83
Not alert	3.01	2.64 to 3.44
Increasing deficit score	1.53	1.47 to 1.59
Increasing time to randomisation	1.00	1.00 to 1.01
OTHER *v* TACS	1.09	0.49 to 2.40
LACS *v* TACS	0.95	0.80 to 1.13
PACS *v* TACS	0.86	0.74 to 1.00
POCS *v* TACS	0.63	0.53 to 0.76
Atrial fibrillation	1.37	1.20 to 1.57
Infarct visible	1.42	1.31 to 1.55

Deficit score, sum of eight possible neurological deficits on presentation, with 0 recorded as 1 and 8 as 7. Age is standardised. A total of 493 patients with not known atrial fibrillation were removed from this analysis.

for the interaction between aspirin or heparin allocation and visible infarction. In this analysis, the two doses of heparin were considered together rather than as two separate groups, and we did not examine any interaction between aspirin combined with heparin treatment. We examined the change in log likelihood on entry of the interaction term into the logistic regression model. There was no evidence of any treatment interaction between visible infarction and either aspirin or heparin allocation and death or dependency at six months (interaction with heparin p=0.7, with aspirin p=0.9)—that is, introducing the interaction term had no effect on the odds ratio for being dead or dependent with or without heparin, aspirin or visible infarction. Interactions between visible infarction and either aspirin or heparin allocation for deaths within 14 days were not statistically significant (interaction with heparin p=0.3, with aspirin p=0.2), but there was a change in the odds ratios for death when the interaction term was added, in the direction of aspirin and heparin both being

Table 5 Previous studies of visible infarction on CT and outcome after stroke. Only studies with a sample size greater than 80 and which examined for an independent association of visible infarction with clinical outcome using multivariate analyses are included. (A) patients scanned up to six hours after stroke, and (B) patients scanned up to two weeks after stroke

Author and year	Sample (n)	CT time window (h) max	Model	Treatment/trial	Prevalence of ischaemic changes	Baseline stroke severity	Stroke subtype	Definition of dependency (or outcome)	Association with dependency
(A) Patients scanned up to six hours after stroke									
Early signs									
Barber 2000[23]	156	3	multivariate	rt-PA	75%	NIH<10 in 30% NIH>20 in 21%	anterior circulation	mRS 3–6 at 3 months	yes ASPECTs score <8
Patel 2001[26]	616	3	multivariate	NINDS	31%	median NIH 13	all subtypes	mRS 2–6 at 3 months	yes marginal, but not with response to rt-PA
v Kummer 2001[25]	786	3	none	ECASS2	57%	mean NIHSS 11,5	hemispheric infarct	mRS 2–6 at 3 months	yes
Buttner 1997[20]	95	6	univariate	unknown	47%	mean SSS 32	MCA Infarct	mRS 2–6 at 4 weeks	yes, but 25% with CT signs had benign course
Censori 1993[3]	172	6	multivariate	unknown	32.4%	9.3% stuporous patients	anterior circulation	mRS 3–5 at 6 months	no
Cornu 2000[24]	1292	6	multivariate	MAST I, ASK, MAST E	27% (5–64%)	21% stuporous patients	all subtypes	mRS at 3 months	no
Manelfe 1999[21]	603	6	multivariate	ECASS I	86,50%	mean SSS 28	hemispheric infarct	mRS 3–6 at 3 months	yes
v Kummer 1997[10]	620	6	multivariate	ECASS I	52%	mean SSS 27,5	hemispheric infarct	mRS 2–6 at 3 months	yes
Trouillas 1998[22]	100	7	multivariate	rt-PA	87,60%	mean SSS 29.3	anterior circulation	mRS 2–6 at 3 months	yes
(B) Patients scanned up to two weeks after stroke									
Established signs									
Moulin 1996[7]	100	14	none	anticoagulants, anitaggregants thrombolysis	94%	mRS at discharge	MCA Infarct	mRS 5–6 at 14 days	yes
Zorzon 1993[27]	80	24	multivariate	unknown	17,5% (HMCA)	unknown	unknown	mRS 4–6 at 1 months	yes (for HMCA)
Candelise 1991[6]	1048	48	multivariate	Italian hemodilution trial	50%	50% severe strokes	all subtypes	death at 6 months	relation to death RR=2
Chamorro 1995[28]	208	72	multivariate	anticoagulants, anitaggregants	41%	mean Matthew 78.4	all subtypes	SOS 4–6 at 10 days	no (but infarct volume)
Rasmussen 1992[2]	210	72	multivariate	unknown	76%	30% somnolent or comatose	all strokes	death at 3 weeks	yes
Saver 1999[29]	191	1 week	multivariate	RANTTAS	69%	median NIH 10	hemispheric infarct	BI <60 or NIH >1 at 3 months	yes (correlation)
Wardlaw 1998[19]	993	2 weeks +	multivariate	antiaggregants	60%	mRS, death and dependency at 6 months d	13% TACI 40% PACI 26% LACI 16% POCI	mRS 3–6 at 6 months	yes (and death)

associated with a lower risk of death in the absence of visible infarction. Thus it is plausible that aspirin and heparin do not work, or are possibly harmful, in patients with a visible infarct. Even in a study of this size, there was not enough power to assess such interactions reliably.

DISCUSSION

This is the largest ever study of the relations between visible infarction on CT, early and late clinical outcome events, and treatment allocation. It is likely to remain the definitive work for some time given its sample size. Therefore, despite the conflicting results of smaller studies, this study demonstrates that the presence of a visible infarct significantly and independently increases the risk of early death and poor long term outcome, after all other major predictors of poor outcome have been accounted for. This conclusion is made more robust by the narrow confidence limits. Thus, despite the scans not being read centrally, or by experts on all occasions (a possible advantage as it is unlikely that all stroke CT scans will ever be read by neuroradiologists), the strength of the relation between CT visible infarction and outcome is still clear.

Even after adjustment for other prognostic factors, visible infarction increased the odds of a poor outcome at six months by 42%. Two thirds of patients with a visible infarct were dead or dependent at six months compared with 53% of patients without a visible infarct, an absolute increase of 13%, or 130 more patients per 1000 with a visible infarct were dead or dependent at six months compared with those without a visible infarct.

What are the drawbacks of this analysis? We used the time to randomisation as a surrogate for time to CT scan as the precise time of CT was not recorded. However, the trial protocol stated that the patient was to be randomised as soon as the CT result was known. It is therefore reasonable to use the time of randomisation as an estimate of the maximum time to CT. Certainly the time of CT could not have been any later than the time of randomisation. The CT scans were not read centrally, but were read by physicians and radiologists in participating hospitals. In fact, this could be considered as a strength rather than a weakness—few CT scans for stroke will ever be read by expert neuroradiologists—there are not enough of them. Clinicians were not specifically trained in CT reading before or during the study. The IST was performed in the first half of the 1990s, before much of the debate on early visible infarction and patient selection for thrombolysis, but at the same time as many of the thrombolysis trials such as the National Institutes of Neurological Disorders and Stroke Trial or the European Cooperative Acute Stroke Study.[25 26] It is possible therefore that the participating physicians/radiologists were less sensitive to identifying subtle signs of early infarction (although the proportion of patients with visible lesions within the first six hours would not support that (fig 1)), and also that some old vascular lesions were inadvertently counted as the relevant new lesion. The fact that about one sixth of patients with a lacunar syndrome scanned within three hours had a visible infarct (fig 1) suggests that, in some cases, an old lesion may have been counted as a new lesion inadvertently because it was in the appropriate area of brain for the patient's symptoms. We regard this as "background noise" and expect that it applied to all subtypes. However, despite this potential degree of over-reporting of infarction, the trends with time within 48 hours and with infarct syndrome are clear cut and robust, and consistent with studies restricting patient entry to within three hours.[26] Finally, our analysis was restricted to patients who had a CT brain scan before randomisation, thus excluding about a third of the total trial cohort. However, as IST was designed to test the value of CT before antithrombotic treatment, a proportion of patients started treatment before CT. We excluded data from the latter as the precise time of CT was not recorded. Knowing that the CT scan must have been done sooner than the randomisation time in the two thirds with prior CT, meant that restricting the analysis to the two thirds was more reliable. Including the third without CT pre-randomisation would have invalidated the results, as in some cases the CT could have been done days after randomisation.

There were comparatively few patients with recurrent fatal or non-fatal haemorrhagic stroke—96 in all—and patients were not rescanned systematically. Haemorrhagic stroke appeared to decline with increasing time from onset. This association may be merely an artefact of case mix. Milder strokes arrive at hospital later than severe strokes[36] and haemorrhagic transformation is more common in large infarcts (which are more likely to be severe strokes) than in small infarcts (mild strokes). More research is needed to sort out the interaction of visible infarction and haemorrhagic transformation, because it may be important for some treatments like thrombolysis. Some thrombolysis trial data suggested that visible infarction is associated with an increased risk of haemorrhagic transformation after thrombolysis,[1] although recent analysis of patients treated within three hours of stroke indicated that visible infarction, although associated with poorer outcome than in patients with no visible infarction, did not independently increase the risk of poor outcome after thrombolysis.[26] It this context, even in this very large dataset, as far as we can tell there was no clear interaction between visible infarction and aspirin or heparin treatment allocation.

What is the next step? Characterisation of patients for stroke severity should take account of visible infarction, as it may usefully modify patient stratification in clinical trials or observational studies. Similarly, prognostic models may be made more accurate by the addition of imaging features. One of the major difficulties in assessing the existing literature (table 5) and in comparing our study with other studies, was the wide range of (and often absent) definitions for good clinical outcome, or of what was meant by infarct signs. These unclear definitions may be partly responsible for the existing confusion over the importance of early infarct signs and the relation with outcome after thrombolysis. A closer look is required at the relation between signs of very early infarction, outcome (both of which should be defined more systematically) and treatment interactions, but with clear definitions of infarct signs and better observer reliability for detection of early infarct signs.

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