full recovery. They subsequently excluded the same groups of patients from the ideal scenario in which all patients were admitted within the time window for thrombolysis. Had thrombolysis actually been given, the outcomes for these patients would have been unknown at the time of administration. These patients should therefore have been included in the analysis.

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1 Jørgensen HS, Nakayama H, Kammersgaard LP, Raaschou HO, Olsen TS. Predicted impact of intravenous thrombolysis on prognosis of general population of stroke patients: simulation model. *BMJ* 1999;319:288-9. (31 July.)

Another trial is needed

Editor—The paper by Jørgensen et al provides a small counterbalance to the enormous propaganda behind an expensive, minimally tested, and potentially harmful intervention.[1] The real ratio of benefit to risk of thrombolytics for stroke may even be far worse than Jørgensen et al calculate, for the following reasons.

Firstly, even fewer stroke patients in community practice would qualify for treatment with alteplase if a strict three hour cut-off point for completion of all diagnostic activities and initiation of the drug were used.

Secondly, inclusion of even a few of those patients with seizure, tumour, infection, etc, whose condition mimics stroke and who constitute perhaps 15-25% of patients diagnosed as having "stroke" in community practice but were rare in the expert based National Institute of Neurological Disorders and Stroke (NINDS) trial,[2] could easily overwhelm any benefits of alteplase, since such patients cannot possibly benefit from treatment but can certainly be harmed.

Thirdly, treatment of even a few patients with subtle haemorrhage, undetected because the computed tomography scan was not read by a neuroradiologist, would have the same effect—and there is good evidence that very few general radiologists, neurologists, or emergency physicians are able to identify most or all such haemorrhages.

Fourthly, treatment outside the specialised environments used in NINDS, and without the experts participating in such studies, could lead to far more harm when a drug that produces such a high rate of intracranial haemorrhage under ideal conditions is used.

Fifthly, of seven trials of lytics in stroke to date, only the fairly small NINDS trial has had positive results—the results of the six that have been either neutral or negative (including several with dramatically increased mortality in patients treated with thrombolytics) are typically ignored.

"Another trial is needed" is a generous summary of the available evidence. Given the extremely limited evidence of efficacy, the marginal nature of that efficacy (under the best of circumstances), and the strong likelihood that such efficacy will not translate into effectiveness in community practice—as well as the real potential for harm—approval of this drug in the United Kingdom, for the treatment of stroke should be withheld unless and until far more definitive evidence (for effectiveness as well as for efficacy) is forthcoming.

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1 Jørgensen HS, Nakayama H, Kammersgaard LP, Raaschou HO, Olsen TS. Predicted impact of intravenous thrombolysis on prognosis of general population of stroke patients: simulation model. *BMJ* 1999;319:288-9. (31 July.)
2 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl Med J* 1995;333:1581-7.

Author's reply

Editor—Our simulation model of intravenous thrombolysis (using alteplase) in patients with acute stroke model had two purposes: firstly, to estimate the target population for intravenous thrombolysis in an unselected population of patients with acute stroke; and, secondly, to estimate the number of patients who would actually benefit from this treatment—provided that the results of the only trial with positive reults so far, the National Institute of Neurological Disorders and Stroke (NINDS) trial,[1] can be reproduced.

In the study we included the 1197 patients from the Copenhagen stroke study, a community based study in which all patients with acute stroke from a well defined catchment area of Copenhagen had all their acute treatment and rehabilitation in one large stroke unit regardless of their age, the severity of the stroke, and their comorbidity prior to stroke. In the first part of our analysis we estimated the target population for alteplase treatment using the inclusion criteria from the NINDS trial. We included patients who eventually died or who recovered fully. A disappointing rate of only 4% of the patients fulfilled the inclusion criteria.

To estimate the number of patients who would have benefited from intravenous thrombolysis we excluded the patients who either recovered fully and had no functional disability after completed rehabilitation or who died during hospital stay. Berwaerts et al argue that these patients should have been included as the outcomes for them would have been unknown at the time of drug administration. We believe, however, that it was justified to exclude them from the analysis of the number of patients who would actually benefit from alteplase treatment. None of these patients would have benefited from treatment because they either had a complete recovery without thrombolysis or they died. As the NINDS trial shows, alteplase treatment has no effect on overall mortality.

The results of our study in combination with the arguments offered by Hoffman should raise serious questions about the approval of intravenous thrombolysis in patients with acute stroke. The possible, but not proved, marginal benefit of intravenous thrombolysis in a very small number of patients (1 out of 160 patients in our simulation model) should be considered in contrast to the marked benefit of treatment and rehabilitation of unselected patients in specialised stroke units,[2–5] regardless of their age, sex, severity of stroke, and comorbidity. Economic resources are limited and should be used where they benefit most patients in the most effective way—in this case by providing early, intensive rehabilitation to all patients in dedicated stroke units.

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1 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl Med J* 1995;333:1581-7.
2 The Stroke Unit Trialists' Collaboration. Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. *BMJ* 1997;315:1151-9.
3 Jørgensen HS, Nakayama H, Raaschou HO, Larsen K, Hübbe P, Olsen TS. The effect of a stroke unit: reduces mortality, discharge to nursing home, length of hospital stay and cost. A community-based study. *Stroke* 1995; 26:1178-82.
4 Jørgensen HS, Kammersgaard LP, Nakayama H, Raaschou HO, Larsen K, Hübbe P, et al. Treatment and rehabilitation on a stroke unit improves 5-year survival. A community-based study. *Stroke* 1999;30:930-3.
5 Jørgensen HS, Kammersgaard LP, Houth JG, Nakayama H, Raaschou HO, Larsen K, et al. Who benefits from treatment and rehabilitation on a stroke unit? A community-based study. *Stroke* 2000;31;434-9.

Intention to treat analysis is related to methodological quality

Editor—In their survey of all randomised controlled trials published in 1997 in four major medical journals, Hollis and Campbell found that only 48% of the reports explicitly mentioned intention to treat analysis.[1] In a considerable proportion it was insufficiently described and sometimes inadequately applied. Their results are confirmed by our assessment of all randomised controlled trials published between 1993 and 1995 in the same four journals.[2] In addition to our assessment of ethical issues, we calculated the proportion of randomised controlled trials reporting intention to treat analysis in accordance with different descriptive and methodological characteristics.

In our review of 608 randomised controlled trials, we found that 290 of the trials (47.7%) explicitly mentioned that they applied the principle of intention to treat analysis. The reporting of this issue increased slightly between 1993 and 1995 (although the increase was not significant). Trials with a greater number of participants and those funded by the pharmaceutical industry were more likely to report the application of the intention to treat principle (table). In the multivariable logistic regression analysis, when we controlled for the general characteristics previously described, we found that trials with survival of patients as the principal outcome were

Reporting of intention to treat analysis in published clinical trials (1993-5)

	Total No	No (%) reporting intention to treat	Crude odds ratio for not reporting the use of intention to treat (95% CI)	Logistic regression multivariable model adjusted odds ratio (95% CI)	Odds ratio (95% CI) adjusted for descriptive characteristics
All sample	608	290 (47.7)			
Descriptive characteristics of the trials					
Journal:					
N Engl J Med	219	122 (55.7)	1	1	
JAMA	81	37 (45.7)	1.50 (0.90 to 2.50)	1.64 (0.92 to 2.92)	
BMJ	105	44 (41.9)	1.74 (1.09 to 2.79)	1.80 (0.96 to 3.39)	
Lancet	203	87 (42.9)	1.68 (1.14 to 2.46)	1.54 (0.95 to 2.50)	
Year of publication:					
1995	211	108 (51.2)	1	1	
1994	195	92 (47.2)	1.17 (0.79 to 1.73)	1.20 (0.78 to 1.86)	
1993	202	90 (44.6)	1.30 (0.89 to 1.92)	1.14 (0.73 to 1.77)	
Country of authors:					
Europe (except United Kingdom)	164	86 (52.4)	1	1	
United Kingdom	127	61 (48.0)	1.19 (0.75 to 1.90)	0.90 (0.52 to 1.55)	
United States	240	120 (50.0)	1.10 (0.74 to 1.64)	1.24 (0.75 to 2.07)	
Other	77	23 (29.9)	2.59 (1.45 to 4.60)	2.59 (1.38 to 4.85)	
Main specialty of authors:					
Medical specialties	432	213 (49.3)	1	1	
Surgery or medical-surgical	106	45 (42.5)	1.32 (0.86 to 2.02)	1.23 (0.76 to 1.99)	
Intensive or emergency care	37	18 (48.6)	1.03 (0.52 to 2.01)	1.08 (0.51 to 2.29)	
Public health	16	7 (43.8)	1.25 (0.46 to 3.42)	1.60 (0.54 to 4.74)	
Other	17	7 (41.2)	1.39 (0.52 to 3.72)	1.29 (0.44 to 3.82)	
Number of participating subjects:					
>500	171	109 (63.7)	1	1	
51 to 500	322	167 (51.9)	1.63 (1.11 to 2.39)	1.68 (1.12 to 2.53)	
⩽50	115	14 (12.2)	12.66 (6.68 to 24.10)	12.43 (6.24 to 24.36)	
Source of funding:					
Pharmaceutical industry	206	129 (62.6)	1	1	
Public agency	165	73 (44.2)	2.11 (1.39 to 3.20)	2.11 (1.34 to 3.34)	
Other	126	52 (41.3)	2.38 (1.52 to 3.75)	2.01 (1.22 to 3.30)	
Not reported	111	36 (32.4)	3.49 (2.14 to 5.68)	2.35 (1.34 to 4.10)	
Methodological characteristics of the trials					
Outcome:					
Survival	142	104 (73.2)	1		1
Other	466	186 (39.9)	4.12 (2.72 to 6.24)		2.86 (1.77 to 4.60)
Sample size estimation:					
Shown	281	167 (59.4)	1		1
Not shown	327	123 (37.6)	2.43 (1.75 to 3.37)		2.28 (1.55 to 3.37)
Compliance with treatment:					
Stated	532	261 (49.1)	1		1
Not stated	76	29 (38.2)	1.56 (0.95 to 2.56)		1.71 (0.98 to 2.99)
Reporting follow up or withdrawals:					
Reporting the number of patients withdrawn or lost to follow up	194	100 (51.5)	1		1
Not giving information about number of patients lost to follow up	414	190 (45.9)	1.25 (0.89 to 1.76)		1.45 (0.98 to 2.14)

A higher odds ratio means a higher probability of not reporting the use of the intention to treat principle.

more frequently reported to follow the intention to treat principle. In addition, those randomised controlled trials that gave no information about sample size were less likely to report the use of this principle (table). Randomised controlled trials not reporting the number of withdrawals or losses to follow up and those not reporting information about compliance with treatment were also less likely to report the intention to treat principle, although these results were not significant.

Our data support the relation between a higher methodological quality of the trials and the reporting of the intention to treat analysis. Our results reinforce the conclusions of Hollis and Campbell that the application of this principle still needs to improve because it seems that there has been no improvement between 1993 and 1997.[1] A joint effort of editors and researchers is needed to meet the CONSORT guidelines[3] and the authors' recommendations favouring intention to treat analysis.[1] A better quality of reporting will help readers to assess the design, conduct, and analysis of randomised controlled trials more critically.

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1 Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;319:670-4. (11 November.)
2 Ruiz-Canela M, Martínez-González MA, Gómez Gracia E, Fernández-Crehuet Navajas J. Informed consent and approval by institutional review board in published clinical trials. *N Engl J Med* 1999;340:1114-5. (Erratum *N Engl J Med* 1999;341:460.)
3 Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;276:637-9.

Using anticoagulation or aspirin to prevent stroke

Research was methodologically flawed

Editor—The paper by Hellemons et al is not justified in concluding that aspirin is the prophylactic choice in primary care for atrial fibrillation, if there is no clear indication for full anticoagulation.[1]

The study is methodologically flawed. As clinicians, we ask ourselves: "Which patient in atrial fibrillation should be given anticoagulants?" This is a statistical question about the risks and benefits of aspirin or warfarin for that individual patient.

In the power calculation Hellemons et al asked whether low anticoagulation (international normalised ratio 1.1-1.6) or aspirin should be used—but this is the wrong question. The choice should have been between aspirin and standard anticoagulation (INR 2.5-3.5). The increased incidence of major intracranial bleeding in the aspirin group compared with the anticoagulated groups (0.75% per patient year *v* 0.35%) calls into question the sagacity of using one tailed statistical tests.

As the study was underpowered, the question of whether standard anticoagulation or aspirin was better in preventing major cerebral infarction cannot be answered. Although there is a trend towards full anticoagulation (hazard ratio 0.67), the 95% confidence intervals are so wide (0.11 to 4.1) that the result is meaningless.

The arbitrary exclusion from standard anticoagulation of all people who were 78 years or older also undermines the study, for although it may have reduced the complication rate from anticoagulation, it will have also reduced the potential benefit.

This paper highlights the problems in reporting "negative" or "no difference" studies. It has failed to show "no difference" between standard anticoagulation and aspirin prophylaxis in atrial fibrillation, as clinically important differences could well exist within the confidence limits. The study adds little to previous work that does demonstrate benefit from anticoagulation[2] and may be misinterpreted as an excuse for