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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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 results so far, the National Institute of Neurological Disorders and Stroke (NINDS) trial,1 can be reproduced.

In our 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 this 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.2–4 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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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.5 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.6 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
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 and may be misinterpreted as an excuse for

Using anticoagulation or aspirin to prevent stroke

Research was methodologically flawed

Entorrn—The paper by Hellemans 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 Hellemans 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 (ENR 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 and may be misinterpreted as an excuse for

References


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