

# Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial)



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## Summary

**Background** Citicoline is approved in some countries for the treatment of acute ischaemic stroke. The drug has shown some evidence of efficacy in a pooled analysis. We sought to confirm the efficacy of citicoline in a larger trial.

**Methods** We undertook a randomised, placebo-controlled, sequential trial in patients with moderate-to-severe acute ischaemic stroke admitted at university hospitals in Germany, Portugal, and Spain. Using a centralised minimisation process, patients were randomly assigned in a 1:1 ratio to receive citicoline or placebo within 24 h after the onset of symptoms (1000 mg every 12 h intravenously during the first 3 days and orally thereafter for a total of 6 weeks [2x500 mg oral tablets given every 12 h]). All study participants were masked. The primary outcome was recovery at 90 days measured by a global test combining three measures of success: National Institutes of Health Stroke Scale  $\leq 1$ , modified Rankin score  $\leq 1$ , and Barthel Index  $\geq 95$ . Safety endpoints included symptomatic intracranial haemorrhage in patients treated with recombinant tissue plasminogen activator, neurological deterioration, and mortality. This trial is registered, NCT00331890.

**Results** 2298 patients were enrolled into the study from Nov 26, 2006, to Oct 27, 2011. 37 centres in Spain, 11 in Portugal, and 11 in Germany recruited patients. Of the 2298 patients who gave informed consent and underwent randomisation, 1148 were assigned to citicoline and 1150 to placebo. The trial was stopped for futility at the third interim analysis on the basis of complete data from 2078 patients. The final randomised analysis was based on data for 2298 patients: 1148 in citicoline group and 1150 in placebo group. Global recovery was similar in both groups (odds ratio 1.03, 95% CI 0.86–1.25;  $p=0.364$ ). No significant differences were reported in the safety variables nor in the rate of adverse events.

**Interpretation** Under the circumstances of the ICTUS trial, citicoline is not efficacious in the treatment of moderate-to-severe acute ischaemic stroke.

**Funding** Ferrer Grupo.

## Introduction

Stroke remains one of the most devastating diseases, often causing death or gross physical impairment or disability.<sup>1,2</sup> In recent years, stroke has been classed as a medical emergency and several clinical trials have been done to find effective therapies. Among pharmacological therapies, two possible treatments exist for acute ischaemic stroke: a fast and complete recanalisation of the occluded artery, and protection of the brain from the ischaemic injury.<sup>3</sup> So far, only thrombolysis with recombinant tissue plasminogen activator (rt-PA), administered within the first 4–5 h after the onset of symptoms, is recommended for the treatment of acute ischaemic stroke.<sup>4</sup>

Recent research suggests that drugs with the potential to enhance endogenous brain plasticity and repair could reduce acute brain damage and improve functional recovery in animal models of stroke, even when they are administered several hours after the ischaemic event.<sup>5,6</sup> One of these new drugs, which might combine neurovascular protection and repair effects, is citicoline. This drug is an exogenous form of cytidine 5'-diphosphate

choline, which is essential for the biosynthesis of membrane phospholipids. Citicoline acts at several levels of the ischaemic cascade and a series of brain repair effects have been reported.<sup>7</sup>

Citicoline has been extensively studied in clinical trials with over 11000 patients and volunteers who have various neurological disorders, including acute ischaemic stroke. In all these studies, citicoline had a similar safety profile as compared with placebo.<sup>8</sup> Despite some post-hoc positive results in subgroups of stroke patients,<sup>9–11</sup> primary endpoints failed to show efficacy. In a pooled analysis with individual patient data of randomised clinical trials, oral citicoline at doses between 500 mg and 2000 mg per day were associated with an odds ratio of 1.33 (95% CI 1.10–1.62) in complete functional and neurological recovery when compared with placebo in patients with moderate-to-severe acute ischaemic stroke.<sup>12</sup> A further meta-analysis of tabulated data confirmed these previous results.<sup>13</sup>

We sought to confirm the results of the pooled data analysis in a large randomised clinical trial based on a

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previous, fully specified hypothesis and analysis. The primary objective of this study was to assess the effects of citicoline compared with placebo on the recovery of patients with moderate-to-severe acute ischaemic stroke at 3 months, after having received 2000 mg daily for 6 weeks.

## Methods

### Study design and patients

This randomised, multicentre, double-blinded, sequential, and placebo-controlled study was approved as appropriate by local or national institutional review boards. Patients were assigned to treatment only after they had given informed consent or, for patients who were unable to do so, after consent had been obtained from an acceptable surrogate.

The trial protocol has been published online. An independent data and safety monitoring committee was responsible for safety reviews and interim analyses based on the primary-endpoint variable. Two independent

contract research organisations (Cenduit, Durham, NC, USA, and Anagram, Barcelona, Spain) were responsible for random allocation of patients, gathering and monitoring data. An external biostatistical office (Bioclever, Barcelona, Spain) stored and checked the data for consistency, then received allocation codes and undertook analyses according to the approved plan.

Baseline assessments included a physical examination, CT or MRI, and the quantification of any neurological deficit with the use of the National Institutes of Health Stroke Scale (NIHSS), a 15-item scale that measures the level of neurological impairment. Total scores on the NIHSS ranged from 0 to 42, with higher values reflecting more severe cerebral infarcts. Patients were also assessed with the NIHSS on days 3 and 7—or at discharge if earlier—after treatment started, and then at weeks 6 and 12. The modified Rankin score (mRs), a measure of disability, was used to assess patients on day 7—or at discharge if earlier—at weeks 6 and 12. Scores on the mRs range from 0 (no symptoms at all) to 6 (death); a score of 5 indicates severe disability (ie, the patient is bedridden and incontinent and requires constant nursing care and attention). Investigators were certified in the use of the NIHSS and mRs. During the follow-up period, the Barthel index was applied to assess the ability of patients to perform activities of daily living on a scale that ranges from 0 (complete dependence on help with activities of daily living) to 100 (independence). This index was scored at weeks 1, 6, and 12. The worst value on the three scales was assigned to patients who died.

Patients were eligible for enrolment if they were 18 years of age or older and had an acute ischaemic stroke referable to the middle-cerebral-artery territory with compatible neuroimaging and onset of symptoms within the previous 24 h. Patients had to score at least eight points on the baseline NIHSS, with at least two of these points from sections five and six (motor), and a prestroke mRs of 0 or 1. The time between hospital admission and randomisation had to be less than or equal to 12 h and the time between randomisation and the administration of the first dose had to be less than or equal to 1 h.

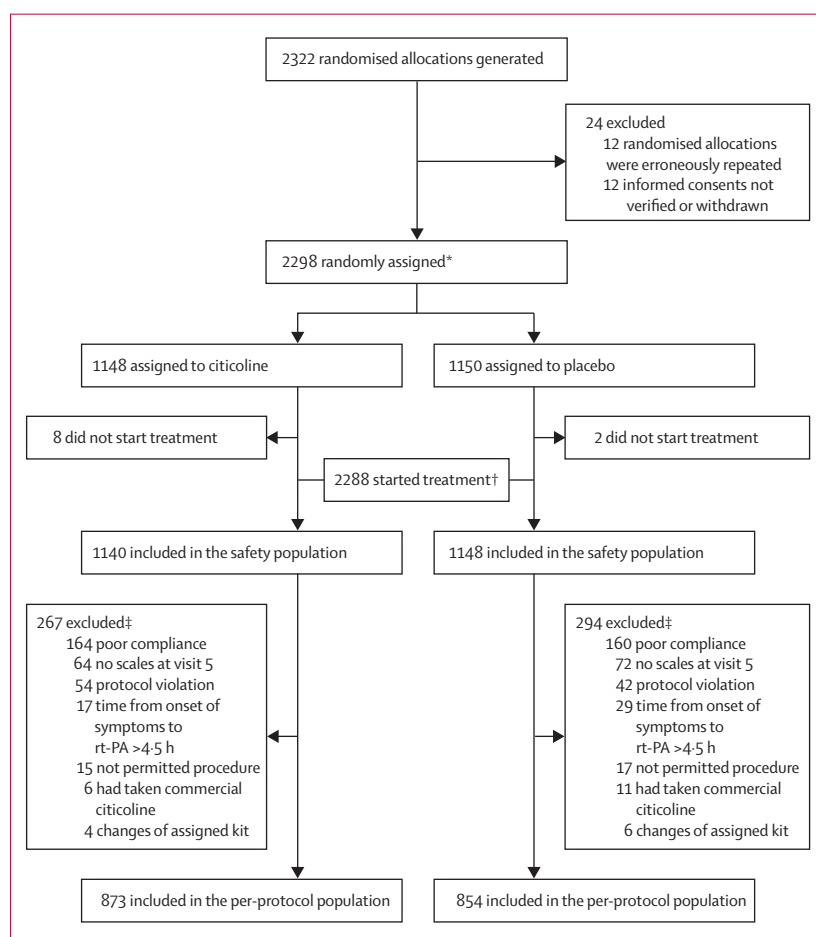
All patients received stroke care according to local treatment practice, including rt-PA for eligible patients presenting within 4·5 h after the onset of the stroke.

This study is registered with ClinicalTrials.gov (NCT00331890).

### Randomisation and masking

Patients were randomly assigned to receive citicoline or placebo for a period of 6 weeks. The randomisation process was centralised using an interactive voice response system (IVRS), under a minimisation process to balance the 1 to 1 ratio between the two groups both overall as well as within every category of the baseline factors: NIHSS (8–14, 15–22, or  $\geq 23$ ); therapeutic window ( $\leq 12$  h or  $>12$  h); intended use of rt-PA (yes or no); age ( $\leq 70$  or  $>70$  years); and side of stroke (right or left

For the **protocol** see <http://www.thelancet.com/protocol-reviews/06PRT-3005>



**Figure 1: Trial profile**

rt-PA=recombinant tissue plasminogen activator. \*The intention-to-treat analysis included all patients who underwent randomisation in the allocated group and their informed consent was available. †After randomisation, one patient in each arm received the alternate treatment. ‡As more than one reason for exclusion from the per-protocol is possible, the total number of reasons is greater than the number of excluded patients.

hemisphere). Once a patient was classed as eligible and informed consent was obtained, the investigator called the IVRS, which registered the patient and provided the kit number to be administered.

Ferrer Grupo (Barcelona, Spain) supplied the study drug and placebo. Citicoline 2000 mg a day was given to patients in the active treatment group in the following way: during the first 3 days, 1000 mg was administered every 12 h in a 100 mL saline solution bag and infused during 30–60 min; from day 4 to the end of the treatment period, two 500 mg oral tablets were given every 12 h. In patients with swallowing problems, tablets were dissolved in 30–60 mL of tepid water and administered through a nasogastric tube.

Patients, researchers, caregivers, individuals assessing the outcomes, data managers, and members of the trial steering committee were masked to group assignment. Placebo was identical and indistinguishable to the active drug in both formats: ampoules and tablets.

In patients returning drugs, poor treatment compliance was predefined as the administration of study drug below 80%. Additionally, patients who received less than 80% of the intravenous dose when it was not followed by immediate oral administration were classed as non-compliers. Poor compliance was not a reason for study withdrawal.

## Procedures

Vital signs were closely monitored for the first 24 h and then at each assessment time. No other cardiovascular or analytical assessment was needed, due to the proven safety profile of citicoline. A follow-up cerebral CT was done when investigators established that baseline CT failed to show evidence of infarction.

To establish whether citicoline had any effect on haemorrhagic transformation after treatment with rt-PA, brain imaging was repeated after 24–36 h in patients receiving concomitant rt-PA. Additionally, brain imaging was repeated when neurological worsening occurred within the first week after enrolment. An independent CT reading panel of two neuroradiologists (Patricia Cuadras and Jaume Capellades; who were unaware of treatment assignments and clinical outcome) assessed baseline and follow-up brain images of patients treated with rt-PA or patients who showed neurological worsening. The procedures for the assessment of the neuroimaging were pre-established in the CT-reading-panel guidelines, annexed to the protocol. Symptomatic intracerebral haemorrhage was defined as blood at any site in the brain on the CT scan (as assessed by the CT reading panel), causing death or an increase in the NIHSS score of 4 or more points. Type of haemorrhagic transformation was classified according to the European-Australasian Acute Stroke Study (ECASS) definition.<sup>14</sup> Neurological deterioration was defined as an increase of 4 or more points in the NIHSS score during the first week. Adverse events and causes of mortality were also recorded.

The primary endpoint was recovery at 90 days as measured by a global test combining the favourable responses from all three outcome scales: Barthel index (95–100), mRs (0–1), and NIHSS (0–1), which were assessed at week 12. Those three components could be interpreted as a multidimensional determination of patient retrieval.<sup>15</sup> This allows a simultaneous global-test analysis<sup>16</sup> with a single interpretation as patient recovery. A similar approach was used in previous studies.<sup>12,17</sup> Further details have been reported elsewhere.<sup>16,18,19</sup>

Secondary objectives were the rate of favourable response in the single scales (mRs, NIHSS, Barthel index), the between-groups comparison of the full distribution of the mRs scores, and the absolute difference in the NIHSS

	Citicoline (N=1148)	Placebo (N=1150)
Age (years)	72.9 (11.8)	72.8 (12.1)
≤70	374 (32.6%)	373 (32.4%)
>70	774 (67.4%)	777 (67.6%)
Sex (female)	560 (48.8%)	596 (51.8%)
Time from stroke onset to treatment (h)	6.5 (4.0–12.3)	6.8 (4.0–12.0)
Time from stroke onset to randomisation (h)		
≤12	911 (79.4%)	916 (79.7%)
>12	237 (20.6%)	234 (20.3%)
NIHSS	15 (11–19)	15 (11–19)
8–14	540 (47.0%)	538 (46.8%)
15–22	552 (48.1%)	556 (48.3%)
>22	56 (4.9%)	56 (4.9%)
rt-PA	532 (46.3%)	532 (46.3%)
Side of stroke—left	519 (45.2%)	532 (46.3%)
Stroke aetiological subtype		
Total non-missing	1128	1123
Large-artery atherosclerosis	258 (22.9%)	229 (20.4%)
Small-vessel disease	60 (5.3%)	61 (5.4%)
Cardioembolic	533 (47.3%)	534 (47.6%)
Undetermined cause	250 (22.2%)	271 (24.1%)
Other cause	27 (2.4%)	28 (2.5%)
Missing	20	27
Medical history		
High blood pressure	841 (73.3%)	830 (72.2%)
Diabetes mellitus	273 (23.8%)	290 (25.2%)
Ischaemic cardiopathy	200 (17.4%)	188 (16.4%)
Atrial fibrillation	405 (35.3%)	417 (36.3%)
Previous transient ischaemic attack	99 (8.6%)	101 (8.8%)
Previous stroke	162 (14.1%)	147 (12.8%)
Current smoker	190 (16.6%)	180 (15.7%)
Excessive consumption of alcohol (>40 g per day)	39 (3.4%)	40 (3.5%)

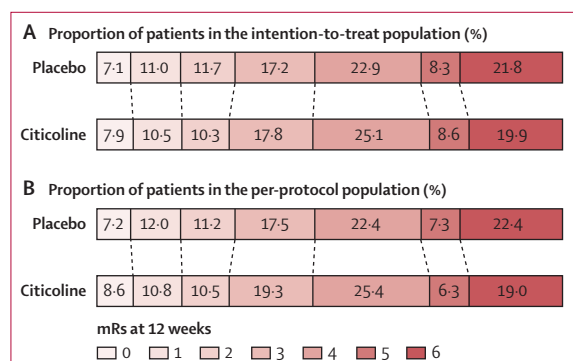
Data are number, number (%), mean (SD), or median (IQR). NIHSS=National Institute of Health stroke scale. rt-PA=recombinant tissue plasminogen activator.

**Table 1: Baseline characteristics**

	Intention-to-treat population			Per-protocol population		
	Citicoline (N=1148)	Placebo (N=1150)	Odds ratio (95% CI)	Citicoline (N=873)	Placebo (N=854)	Odds ratio (95% CI)
<b>Primary endpoint</b>						
Global outcome	..	..	1.03 (0.86–1.25)*	..	..	1.05 (0.84–1.31)†
<b>Secondary analyses</b>						
Shift analyses of mRs	..	..	1.02 (0.88–1.19)‡	..	..	1.10 (0.93–1.30)‡
<b>Individual scales</b>						
mRs ≤1§	211 (18.4%)	208 (18.1%)	1.07 (0.85–1.36)	169 (19.4%)	163 (19.2%)	1.04 (0.79–1.36)
NIHSS ≤1§	264 (23.0%)	260 (22.6%)	1.09 (0.87–1.36)	209 (24.1%)	190 (22.3%)	1.17 (0.91–1.51)
Barthel index ≥95§	307 (26.7%)	321 (27.9%)	0.95 (0.77–1.17)	250 (28.8%)	246 (28.9%)	1.01 (0.79–1.28)

Percentages represent success for the dichotomised scales. mRs=modified Rankin score. NIHSS=National Institutes of Health stroke scale. \*Odds ratio adjusted for the sequential design and minimisation factors and centre. †Odds ratio adjusted for minimisation factors. ‡Cumulative ordinal logistic regression for the entire scale distribution (adjusted odds ratio). §Unadjusted odds ratio.

**Table 2: Odds ratios for primary and secondary endpoints at 90 days**



**Figure 2: Shift analysis of the modified Rankin score**  
 Common estimate of the odds ratio of improvement over the six possible cutpoints are 1.02 (95% CI 0.88–1.19) in the intention-to-treat population (A) and 1.10 (0.93–1.30) in the per-protocol population (B). mRs=modified Rankin score.

between baseline and 3 months. As a post-hoc analysis, and in accordance with reviewers' recommendations, and CONSORT guidelines, we updated the previous tabulated meta-analysis for acute ischaemic stroke,<sup>13</sup> which defined success as mRs 0–2.

The safety endpoints included death, serious adverse events and non-serious adverse events, vital signs for all patients, and follow-up neuroimaging data for patients receiving rt-PA or with neurological worsening. Also, we assessed citicoline safety and tolerability on the basis of the following parameters: blood pressure during the first 3 days of treatment and week 1 (or discharge), and adverse events reported by investigators.

### Statistical analysis

Statistical analyses followed the protocol and the intention-to-treat principle with no deviations. Analyses were fully specified in a statistical analysis plan before treatment allocation was provided.

Statistical analyses for primary (global) endpoint were based on logistic regression adjusted for minimisation factors (baseline NIHSS, therapeutic window, use of rt-PA, location of stroke, age, and centre) and sequential

design. We used a group sequential design using a modified version of the triangular test.<sup>16</sup> For each individual efficacy measure (NIHSS, mRs, and Barthel index), two summary statistics (Z and V) were calculated. The Z statistic measured how much better citicoline was than placebo, with a positive value indicating that citicoline was better. The V statistic measured how much information was contained in the recorded data regarding the treatment difference. The global test was constructed by combining the three separate analyses together to assess the combined evidence for the efficacy of citicoline.

Secondary (individual) endpoints were adjusted for minimisation factors. The distribution of the mRs scores was analysed by cumulative ordinal logistic regression, which provides a common estimate for the odds ratio over any possible cutpoint.

Efficacy analyses of the intention-to-treat population used the last observation carried forward (LOCF) data set. This dataset consists of data recorded or carried forward from the most recent visit, either week 6, week 3, or at baseline if no data were recorded at week 12 but patients were still alive. Any exclusion from this population as well as any imputed value to deaths, cross-in, and drop-outs was decided by the trial steering committee before unmasking. Patients who had died within 12 weeks (or were lost to follow-up without evidence that they were still alive) were recorded as failures on all three scales.

Efficacy analyses of the per-protocol population included all patients who were randomly assigned, had at least one efficacy assessment after receiving at least one dose of study drug and who met all inclusion criteria and none of the exclusion criteria. This sample was made with the dataset from observed cases, consisting of only the actual data recorded at each visit. This dataset was used to investigate the potential for bias in the results due to replacement of missing data in the LOCF dataset.

In accordance with recommendations of the reviewers of the report and specific reporting guidelines,<sup>20</sup> we did separate post-hoc unadjusted tests for interaction

See Online for appendix

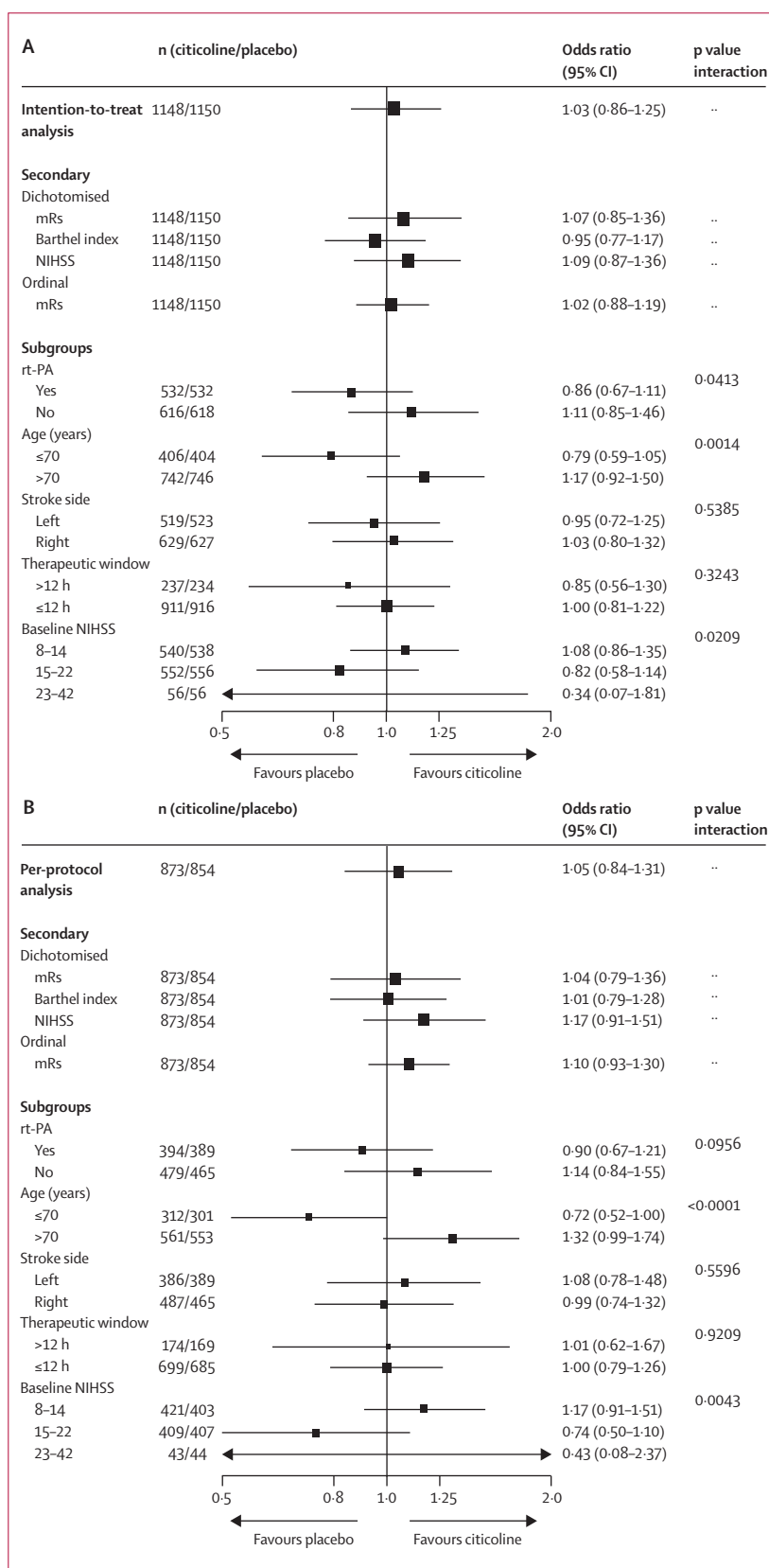
between the treatment and each minimisation factor on the basis of Cochran's *Q* statistic. For the safety analysis, patients were classed as treated. The study was designed to have an 80% chance of establishing the superiority of citicoline if the true log odds ratio (citicoline *vs* placebo) was  $\log(1.26)=0.231$ , a conservative value within the 95% CI obtained in the pooled analysis,<sup>12</sup> using a two-sided 5% significance level. Initially, four interim analyses were planned (and a final analysis) to be done when the 12-week assessments were available (ie, when 1000, 1533, 2067, and 2600 patients were recruited). At each interim analysis, the data safety and monitoring board reviewed unmasked data for patient safety and undertook the planned analysis to give one of three formal recommendations according to criteria described elsewhere.<sup>16</sup> After the second interim analysis, which included 1532 patients, the trial steering committee noted from the masked data that the overall event rate was lower than anticipated and that the recruited population were 4 years older on average, it had more severe stroke (2 points in median NIHSS) and that a higher rate of rt-PA had been used. The data and safety monitoring board noted with masked data that the correlations between the test statistics were higher than expected (appendix p 1) and recommended increasing the maximum study sample by 750 patients to restore power to 80%. If no boundary was reached at the third and fourth analyses, then the study would continue to a fifth and final analysis based on 3350 patients. The protocol was amended in accordance with this recommendation. Protocol amendment did not include any change in eligibility criteria nor clinical outcomes nor statistical analysis. On Oct 21, 2011, the data and safety monitoring board did the third interim analysis, based on complete data for 2078 patients, and found that the statistical stopping boundary for futility had been crossed. The board recommended that the trial steering committee stop recruitment, without explaining the reason, and that they finish the follow-up for the 220 already randomly assigned patients. When all the recruited patients completed their follow-up, and once the database was closed, the data and safety monitoring board did the final analysis on 2298 patients and reported the results to the trial steering committee.

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Two academic authors (AD and EC)

**Figure 3: Forest-plot of all the outcomes**

Odds ratios for primary and secondary outcomes and subgroup analyses of minimisation factors for main outcome: (A) intention-to-treat population; and (B) per-protocol population. Numbers of successes for the three endpoints for both groups are shown in table 2, and numbers regarding the ordinal (shift) analysis are shown in figure 2. Numbers for the subgroup analysis are shown in the appendix. mRs=modified Rankin score. rt-PA=recombinant tissue plasminogen activator. NIHSS=National Institutes of Health stroke scale.





guaranteed the veracity and completeness of the data analyses. The trial steering committee had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Patients were enrolled into the study from Nov 26, 2006, to Oct 27, 2011. 37 centres in Spain, 11 in Portugal, and 11 in Germany recruited patients. Of the 2298 patients who gave informed consent and underwent randomisation, 1148 were assigned to citicoline and 1150 to placebo (figure 1). All patients were included in the intention-to-treat population. The treatment was not given to eight patients assigned to citicoline and two assigned to placebo, in general because of delays in recognising whether or not the patient met the eligibility criteria. In no cases did the investigators become aware of the study group that was assigned to these patients.

The mean age of the trial population was 72·9 (SD 12·0) years. As expected, both study groups were well-balanced with respect to baseline minimisation factors, but also with regard to the following factors: previous medical history; tobacco and alcohol consumption (table 1); demographics; patient baseline vital signs; and serum glucose (data not shown).

A total of 561 (24%) of 2298 patients showed protocol deviations (267 citicoline vs 294 placebo; figure 1). After exclusion of these patients in each group, the resulting number of patients were selected for the per-protocol analysis.

A total of 859 (75%) of 1148 patients in the citicoline group and 838 (73%) of 1150 in the placebo group completed the 90-day follow-up. 225 (20%) of 1148 patients in

the citicoline group and 241 (21%) of 1150 in the placebo group died before the 90-day follow-up. The worst value was imputed, respectively, to three (<1%) of 1148 patients in the citicoline group and ten (1%) of 1150 patients in the placebo group who were lost to follow-up and could not be verified as still alive. LOCF was imputed to 64 (6%) of 1148 citicoline patients and 72 (6%) of 1150 placebo patients who were alive and had no follow-up scale assessment at day 90.

Global recovery at 90 days was similar in both groups. The median unbiased estimate of the adjusted odds ratio of the primary efficacy endpoint was 1·03 (95% CI 0·86–1·25). The odds ratios were also neutral in the subgroups defined by the minimisation factors. Similar results were reported in the secondary objectives (table 2). Shift analysis showed a similar distribution of scores on the mRs at 90 days in both groups (figure 2). The common estimate of the citicoline improvement effect across any scale cutpoint was odds ratio 1·02 (95% CI 0·88–1·19). In the analysis of the per-protocol population, no benefit from citicoline over placebo was reported, neither in the primary-efficacy endpoint nor in the secondary endpoints (table 2, figure 2). NIHSS score improved from baseline in the intention-to-treat population (raw mean –1·54 [SD 13·61]) and in the placebo group (mean 0·89, SD 14·34), resulting in an effect size adjusted by minimisation factors of 0·62 (95% CI –0·49 to 1·73;  $p=0\cdot27$ ). In the per-protocol population, the raw average improvement in the NIHSS score was –2·18 (SD 13·37) in the citicoline group and –0·91 (14·51) in the placebo group, with an effect size of 1·26 (95% CI –0·01 to 2·53;  $p=0\cdot051$ ).

Significant results for the heterogeneity of the treatment effect among subgroups were reported (figure 3). The effect of citicoline appeared more beneficial for patients older than 70 years of age than for those aged 70 years or younger ( $p=0\cdot001$ ); for patients with moderate stroke severity (NIHSS <14;  $p=0\cdot021$ ); and for patients not treated with rt-PA ( $p=0\cdot041$ ). These results were similar both in the secondary per-protocol population (figure 3) and in sensitivity generalised-estimating-equation analyses (data not shown).

Mortality was comparable between the two groups (221 [19%] of 1148 patients in the citicoline group vs 242 (21%) of 1150 in the placebo group;  $p=0\cdot31$ ). Adverse events were also similar in both groups (4903 total events in the citicoline group vs 4923 in the placebo group, affecting 1064 patients in the citicoline group vs 1080 in the placebo group; table 3, appendix pp 2–28). Neurological worsening, as defined by the protocol, was reported in 184 (16%) of 1148 patients in the citicoline group and in 204 (18%) of 1150 patients in the placebo group.

Follow-up CT or MRI examinations were available for the CT-reading-panel assessment of 1003 patients from a total of 1065 treated with rt-PA (497 in the citicoline and 506 in the placebo group). Haemorrhagic transformation assessed by the CT reading panel occurred in 112 (23%)

	Citicoline (N=1140)	Placebo (N=1148)
<b>Serious adverse events</b>		
Haemorrhagic or ischaemic stroke	59 (5·2%)	52 (4·5%)
Cardiac disorders	45 (3·9%)	39 (3·4%)
Pneumonia	31 (2·7%)	31 (2·7%)
<b>Other adverse events</b>		
Cardiac disorders	277 (24·3%)	295 (25·7%)
Pyrexia	258 (22·6%)	254 (22·1%)
Constipation	245 (21·5%)	239 (20·8%)
Urinary tract infections	219 (19·2%)	207 (18·0%)
Headache	154 (13·5%)	160 (13·9%)
Nausea and vomiting symptoms	153 (13·4%)	162 (14·1%)
Agitation	125 (11·0%)	104 (9·1%)
Haemorrhagic transformation stroke	91 (8·0%)	93 (8·1%)
Pneumonia	68 (6·0%)	67 (5·8%)
Hypotension	48 (4·2%)	52 (4·5%)
Ten patients who were randomly assigned were not treated. See appendix for every reported adverse event.		
<b>Table 3: Most relevant or frequent adverse events reported during the study</b>		

of 497 patients receiving rt-PA and citicoline together and in 113 (22%) of 506 of those receiving rt-PA and placebo ( $p=0.98$ ). Symptomatic haemorrhagic transformation occurred in 30 (6%) of 497 patients who received citicoline and 40 (8%) of 506 patients assigned to placebo ( $p=0.25$ ). Type of haemorrhagic transformation was comparable between groups.

## Discussion

The ICTUS trial included a large sample of patients with moderate-to-severe acute ischaemic stroke of the anterior territory. The randomisation process balanced the two groups well with regard to the prognostic factors. As the trial was rigorously undertaken and was powered to detect an odds ratio of 1.26, we can conclude that either there is no treatment effect, or there is a decreased magnitude of the estimated treatment effect in previous meta-analyses, or the trial design lacked sensitivity to raise such a treatment effect. In any case, the ICTUS trial has been unable to confirm the efficacy of citicoline.

Some other factors could have reduced the sensitivity of the ICTUS trial (eg, poor treatment compliance; use of concomitant non-protocol drugs, which potentially interfered with treatment response; missing scale values at day 90; and inclusion criteria protocol violations). However, per-protocol analyses of 75% of the total population who fulfilled all the protocol criteria obtained similar results.

The pooled meta-analysis of previous randomised trials with citicoline showed promising results,<sup>12</sup> with an increased probability of global recovery at day 90. Furthermore, results were also positive in the individual mRs and Barthel index scales. The ICTUS trial followed a protocol nearly identical to that of the pooled meta-analysis, with minimal differences in statistical analysis. Indeed, the sample rationale and the statistical design were built to replicate the results of the meta-analysis.<sup>12</sup> However, none of the benefits were confirmed in the ICTUS study. We updated the tabulated data meta-analysis (figure 4) that showed an overall significant effect of citicoline (odds ratio 1.14, 95% CI 1.00 to 1.30) and a significant heterogeneity of effects ( $p=0.0029$ ) between the previous studies and the ICTUS trial. These discordant results have several possible explanations, because there were important differences between the two study samples.

The trials were done 10 years apart, a period of time in which the standard of stroke care has improved substantially; patients randomly assigned in the ICTUS trial were on average 4 years older, they had more severe strokes (median NIHSS 15 [IQR 11–19] in the ICTUS trial vs 14 [IQR 10–18] in previous trials), and they were more frequently treated with rt-PA (47% in the ICTUS trial vs 13% in the previous trials). Since only patients with NIHSS score of 8 or higher were randomly assigned, substantial dilution of effect by stroke mimics was unlikely. We cannot rule out a ceiling effect resulting

from an already maximal improvement due to rt-PA use. The issue of enrolling rt-PA treated patients into stroke trials is controversial.<sup>23,24</sup> Thus, the conflict between our results and the evidence obtained in previous meta-analyses<sup>12,13</sup> should be interpreted in the context of a lack of citicoline effect when it is used in addition to the best medical treatment (panel). Finally, we cannot rule out that treatment up to 24 h after stroke could dilute any beneficial effect of the drug. On the other hand, as the updated

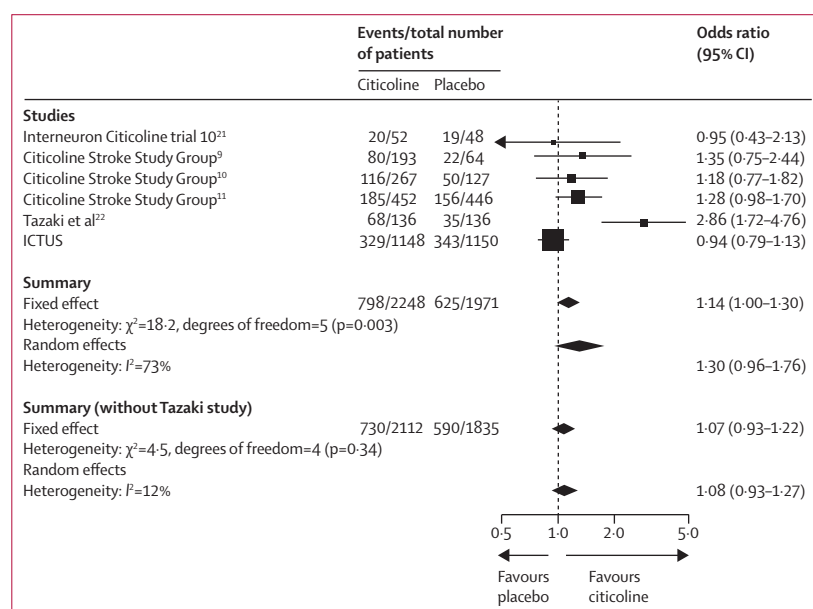


Figure 4: Forest plot for the updated tabulated meta-analysis

Success is defined as modified Rankin score of 0, 1, or 2.

## Panel: Research in context

### Systematic review

We searched Medline, Embase, and the Cochrane Library for reports published in English before May 9, 2012, with the following search terms: "CDP-choline" or "citicoline"; "acute ischemic stroke" or "acute cerebral infarction"; and "randomized clinical trial". We did not identify any new, randomised controlled clinical trials of citicoline for the treatment of acute ischaemic stroke that were not previously included in the meta-analysis by Saver.<sup>13</sup> In this meta-analysis, patients receiving citicoline had substantially reduced frequencies of death and disability. We have updated this meta-analysis adding ICTUS trial results on recovery as measured by a modified Rankin score of 0 to 2. We have not assessed haemorrhagic stroke and have not included very old trials, because Saver<sup>13</sup> highlighted a significant heterogeneity with smaller, lower-quality score trials that tended to show more favourable effects than larger, higher-quality score trials.

### Interpretation

On top of the best treatment, citicoline does not show any clinical improvement but, as shown in the updated fixed-effects meta-analysis (figure 4), the effect of the drug remains significant (odds ratio 1.14, 95% CI 1.00-1.30). Heterogeneity coming from the older studies suggests that the beneficial effect of citicoline over time was diluted in parallel with the improvement of the standard of care of acute ischaemic stroke. The distinct effects of citicoline in three of five prespecified subgroups cannot be explained by selective outcome reporting nor by multiplicity analyses. Further analyses are needed to clarify these results.

meta-analysis is no longer significant, if we exclude the more positive and older study, previous meta-analyses could have overestimated the treatment effect.

Additionally, patients with the most severe strokes and large acute ischaemic lesions on CT or MRI were not excluded from the trial. Citicoline treatment effect might have been diluted by the inclusion of patients with established large irreversible infarction.

The potential role of these factors in diluting the citicoline effect could be supported by the results from the subgroup analysis. We have obtained some evidence of interaction that might suggest a distinct effect of citicoline in patients older than 70 years of age, in those with moderate stroke severity, and in patients not treated with rt-PA. However, this interpretation has the weakness of multiplicity analyses and a serious drawback, since if we want to accept that citicoline has a positive effect on those subgroups, we should also be willing to accept that it has a negative effect in others. In any case, those results require further comprehensive analyses.

The prespecified assessment of neuroimaging data by the CT reading panel included haemorrhagic transformation in patients treated with rt-PA and in those with neurological worsening. In both treatment groups the rate of haemorrhagic transformation and symptomatic intracerebral haemorrhage was comparable, so we did not find any significant citicoline effect on the haemorrhagic risk of rt-PA.

The previous pooled analysis<sup>12</sup> reported on the overall similar safety of citicoline and placebo, yet with a more frequent rate of anxiety and leg oedema but lower frequency of depression, falling down, and urinary incontinence. However, in the ICTUS trial the numbers and types of adverse events and serious adverse events, including neurological events, were similar in the two groups.

In conclusion, under the circumstances of the ICTUS trial, citicoline is safe but is not efficacious in the treatment of moderate-to-severe acute ischaemic stroke.

#### Contributors

AD, JAS, JC, ED-T, JF, EM-V, EC, and JJS contributed equally in the study design, data analysis, data interpretation, and writing the report. AD, JAS, ED-T, JS, TS, VTC, and JM contributed in the collection of data, representing the most active centres. All the authors reviewed and approved the Article.

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#### Conflicts of interest

AD and EC have received consultant fees and honoraria as chairman and statistician, respectively, of the trial steering committee; and honoraria for giving lectures for Grupo Ferrer. JAS, JC, ED-T, JF, and EM-V have received consultant fees and honoraria from Ferrer Grupo as members of the trial steering committee. JAS, ED-T, EM-V, JS, TS, and JM have received honoraria for giving lectures for Ferrer Grupo. VTC



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