Citocoline for Acute Ischemic Stroke: A Systematic Review and Formal Meta-analysis of Randomized, Double-Blind, and Placebo-Controlled Trials

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Citicoline for Acute Ischemic Stroke: A Systematic Review and Formal Meta-analysis of Randomized, Double-Blind, and Placebo-Controlled Trials

Julio J. Secades, MD, PhD,* José Alvarez-Sabín, MD, PhD,† José Castillo, MD, PhD,‡ Exuperio Díez-Tejedor, MD, PhD,§ Eduardo Martínez-Vila, MD, PhD,‖ José Ríos, MSc,¶ and Natalia Oudovenko, PhD*

Background: Citicoline is a drug approved for the treatment of acute ischemic stroke. Although evidence of its efficacy has been reported, recently published results of a large placebo-controlled clinical trial did not show differences. This study aims to assess whether starting citicoline treatment within 14 days after stroke onset improves the outcome in patients with acute ischemic stroke, as compared with placebo. Methods: A systematic search was performed to identify all published, unconfounded, randomized, double-blind, and placebo-controlled clinical trials of citicoline in acute ischemic stroke. Results: Ten randomized clinical trials met our inclusion criteria. The administration of citicoline was associated with a significant higher rate of independence, independently of the method of evaluation used (odds ratio [OR] 1.56, 95% confidence interval [CI] = 1.12-2.16 under random effects; OR 1.20, 95% CI = 1.06-1.36 under fixed effects). After studying the cumulative meta-analysis, and with the results obtained with the subgroup of patients who were not treated with recombinant tissue plasminogen activator (rtPA) (OR 1.63, 95% CI = 1.18-2.24 under random effects; OR 1.42, 95% CI = 1.22-1.66 under fixed effects), our hypothesis of dilution of the effect of citicoline was confirmed. When we analyzed the effect of citicoline in patients who were not treated with rtPA and were receiving the highest dose of citicoline started in the first 24 hours after...
Introduction

Despite global and regional health crises, global life expectancy has increased continuously and substantially over the past 40 years. This is associated with an increase in incidences of age-related diseases, such as ischemic stroke. Stroke is the second leading cause of death in the world, and since 1990, a 26.5% increase in ischemic stroke mortality has been reported, with a parallel increase in the rates of disability.

Only in recent years have advances allowed for relevant improvement in the outcome of this devastating disease. A new era in acute stroke care began in 1995, when it was shown that early intravenous administration of recombinant tissue plasminogen activator (rtPA) improved outcome in a carefully selected patient group with acute ischemic stroke. Together with the use of rtPA, treatment in stroke units (SUs), the early use of aspirin, and decompressive surgery are recognized as therapies with proven efficacy in the management of acute ischemic stroke. Thus, very early treatment with rtPA in an SU can be considered the gold standard, but can only be applied in a qualified center, in developed countries. However, the use of rtPA remains very low in the world, and there are substantial differences in the standard of care for acute ischemic stroke. Obviously, there is an urgent need for available therapeutics for acute stroke.

Citicoline, or CDP-choline, a drug that combines neurovascular protection and repair effects, has been used to treat acute ischemic stroke and other neurological disorders, with an excellent safety profile. In 2002, a formal meta-analysis of trials of CDP-choline in acute and subacute stroke suggested a beneficial and substantial treatment effect, with absolute reductions of 10%-12% in the rates of long-term death and disability. In a pooled data analysis (PDA), the odds ratio (OR) of complete functional and neurological recovery in patients with moderate-to-severe acute ischemic stroke treated with oral citicoline for 6 weeks was 1.33 (95% confidence interval [CI] = 1.10-1.62) when compared with placebo. A further updated meta-analysis of tabulated data confirmed these previous results, with a reduction in death or dependency (OR = 0.65, 95% CI = 0.54-0.77; P = .00001; Number Needed to Treat 9.5).

The recent ICTUS trial could not confirm the efficacy of citicoline against placebo as an add-on therapy on top of the best standard of care. Also in the ICTUS trial, it was hypothesized that the beneficial effect of citicoline over time was diluted in parallel with improved standards of care for acute ischemic stroke.

For this reason, we decided to perform an exhaustive and systematic search for all double-blind and placebo-controlled clinical trials performed with citicoline worldwide, and to conduct an updated meta-analysis to assess if treatment with citicoline (started within 14 days after stroke onset) improves the outcome (measured as a modified Rankin Scale [mRS] score of 0-2 or equivalent) in patients with acute ischemic stroke when compared with placebo.

Methods

Protocol and Registration

The present systematic review and meta-analysis are based on a pre-existing protocol, adapted from a published protocol in The Cochrane Library. The protocol has been submitted and registered at the PROSPERO register, with registration number CRD42013005070.

Eligibility Criteria

Clinical trials that were double-blind, randomized, and controlled with placebo were included. No restrictions regarding language, publication date, or publication status were applied. Only trials in which the active study agent was CDP-choline were included, and trials comparing CDP-choline treatment with any other active treatment were excluded.

All trials randomizing patients of any age or sex were included, with index events of ischemic stroke and/or presumed ischemic stroke (in studies without neuroimaging), and with randomization occurring within 14 days after stroke onset. This broad treatment time window of 14 days was chosen because citicoline may have effects at different stages in the evolution of ischemic brain injury and repair. No restrictions were applied in regard to doses, route of administration, or duration of treatment.

The primary efficacy measure was patient independence at the end of a scheduled follow-up period.

Information Sources

Studies were identified by searching electronic databases, scanning reference lists of articles, and consulting with experts in the field and at the drug company (Ferrer Group).
The search was applied to:
- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, latest issue);
- MEDLINE (1966 to present);
- PubMed (1940s to present);
- Embase (1974 to present);
- Internet Stroke Center (stroke trials registry); and
- National Institute of Health (ClinicalTrials.gov).

Also, an exhaustive search on the Internet and in the bibliographic database of Ferrer Group was performed to detect studies published in journals that were not indexed or included in databases.

**Search Strategy**

The following search strategy for MEDLINE was used and modified for the other databases when necessary.

**MEDLINE**
1) cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp “intracranial embolism and thrombosis”/ or stroke/ or exp brain infarction/ or cerebral infarction/
2) ((maintain ischaemic or ischemic) adj5 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.
3) ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracranial or infratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4) 1 or 2 or 3
5) CDP-choline or cytidine diphosphate choline or citicoline
6) (choline or (cytidine adj5 diphosphocholine) or cytidine diphosphate choline or CDP-choline or citicoline or citicholine or cidifos).tw.
7) 5 or 6
8) 4 and 7
9) limit 8 to humans

The search in Cochrane CENTRAL, Clinicaltrials.gov, and Internet Stroke Center was performed using the term “CDP-choline” or “citicoline.” The broad search on the Internet and PubMed was performed using the term “CDP-choline OR citicoline-5′-diphosphocholine OR cytidine-5′-diphosphate choline OR citicoline OR citocholine.” The search in the bibliographic database of the Ferrer Group was performed using the terms “CDP-choline or citicoline and stroke.”

**Selection of Studies**

Two review authors (J.J.S. and N.O.) reviewed the abstracts of articles retrieved in the search. Full-length papers for any possible abstract that met the inclusion criteria were obtained. Five review authors (J.J.S., J.A.S., J.C., E.D.T., and E.M.V.) reviewed all retrieved papers to identify those trials that met the inclusion criteria for the review.

**Data Extraction and Management**

Two review authors (J.J.S. and N.O.) independently extracted the efficacy data from eligible trials. These review authors resolved discrepancies through discussion with other authors (J.A.S., J.C., E.D.T., and E.M.V.) and by referencing the original report.

**Data Items**

The primary efficacy measure was patient independence at the end of the scheduled clinical trial follow-up. If available, the mRS was used for this measure (mRS score of 0-2). In studies where the mRS measure was not available, we used the most comprehensive measure of disability or handicap available from the trial.

The information was checked for the doses used, the route of administration, and the duration of treatment with CDP-choline.

**Assessment of Risk of Bias in the Included Studies**

The methodological quality of the selected studies was assessed using The Cochrane Collaboration’s tool for assessing the risk of bias. Each of the following points was scored as “yes,” “no,” or “unclear” (where “yes” indicates that the study is less open to bias):

1) Method of randomization (selection bias)
2) Concealment of allocation (indication bias)
3) Blinding of investigators and patients (performance bias)
4) Blinding of outcome assessment (detection bias)
5) Adequate follow-up (attrition bias)
6) Other possible bias

Based on these criteria, we divided the studies into the following 3 categories:

- **A**—all quality criteria met: low risk of bias,
- **B**—one or more of the quality criteria only partly met: moderate risk of bias, and
- **C**—one or more criteria not met: high risk of bias.

To avoid selection bias, only studies categorized as C were rejected. Other studies not included were those performed for other indications, such as hemorrhagic stroke and those not reporting independence as an outcome.

**Measures of Treatment Effect**

Dichotomous statistical meta-analytic methods were used, and the Mantel–Haenszel method was applied for the estimation of OR in fixed effects and DerSimonian–Laird for random effects to calculate the global treatment effect.
Data Synthesis

The formal meta-analysis was performed using the rmeta package\(^a\) of the R software\(^b\).

Hypothesis of statistical heterogeneity was quantified by means of an $\hat{P}$ value defined as $100\% \times (Q - df)/Q$, where $Q$ is Cochran's heterogeneity statistic and $df$ the degrees of freedom and their $P$ value. $\hat{P}$ values of the random effects represent the percentage contribution of a given random effect to the overall heterogeneity. Values of $\hat{P}$ around 25%, 50%, and 75% can be considered as low, moderate, and high levels of heterogeneity, respectively.\(^30\) End points from individual studies were analyzed to compute individual and pooled OR with their 95% CI, by means of a random-effects model (which accommodates clinical and statistical variations better).

To explore the hypothesis of a diluted effect of citicoline in parallel with the improvement of the standard of care of acute ischemic stroke, we used the cumulative meta-analysis. In cumulative meta-analysis, experiments are accumulated from the earliest to the latest, where each successive experiment includes a synthesis of all previous experiments. This chronological combination of the experiments allows us to show if there is a consistency in the results of consecutive experiments and indicate if the results continually favor 1 process, product, or treatment.

The analyses were performed separately by J.J.S. and J.R. Then the results were compared for discrepancies.

Risk of Bias across Studies

As presumed, heterogeneity existed among the studies performed over 4 decades; so, the main analysis used the random-effects model to determine if the effects of CDP-choline were statistically and significantly different from the control group. As there is evidence of between-study heterogeneity ($\hat{P} > 50\%$), we compared the fixed-effects and random-effects estimates of the intervention effect.\(^31\)

Additional Analyses

There were nonprespecified subgroup analyses. In the sensitivity analysis, we performed the same analyses with the rtPA-treated patients excluded, as rtPA can be considered responsible for the ceiling effect and because, in the ICTUS trial,\(^28\) a significant interaction with the use of rtPA was detected. Because the percentage of stroke patients who are treated with rtPA is, in general, very low,\(^15\) this analysis is convenient and allows a more realistic estimation of the effect of citicoline when compared to the most usual acute care. Another additional analysis was based on patients not treated with rtPA and who began the highest dose of citicoline (2 g/day/6 weeks) within the first 24 hours after onset, which was the dose showing efficacy in the PDA\(^20\) and the dose used in the ICTUS trial,\(^28\) reflecting a more contemporary standard of care, as the studies are more recent.

To report this systematic review, we followed the PRISMA statement.\(^32\)

Results

Study Selection

Searching the Embase database provided 1219 documents, with 45 documents on acute stroke. Searching the MEDLINE database provided 350 documents, with 27 documents on acute stroke. Searching the Cochrane CENTRAL provided 166 documents, with 29 documents on acute stroke without duplicates. Searching the PubMed database provided 1983 documents, with 24 documents on acute stroke. Searching ClinicalTrials.gov provided 33 documents, with only 1 completed study on acute ischemic stroke. Searching the Internet Stroke Center provided 10 documents, with 5 completed studies on acute ischemic stroke. Searching the Ferrer Group database provided 243 documents, with 33 documents on acute stroke without duplicates. The studies were selected after reviewing the citation, the abstracts, and the full papers when available. Compiling all the results, 63 studies on acute stroke were selected to be fully reviewed for inclusion in the systematic review (Fig 1). Among the 63 studies selected, only 10 fulfilled the criteria to be included in the systematic review and meta-analysis. The reasons for excluding the 53 studies were as follows:

- Study categorized as C: 37\(^{33-69}\)
- Duplicated publications: 3\(^{70-72}\)
- Study not C but compared with an active drug: 4\(^{73-76}\)
- Study not C but no independence data were available: 3\(^{77-79}\)
- Study not C but in hemorrhagic stroke: 2\(^{80,81}\)
- Study not C but other investigational product: 4\(^{82}\)
- Study not C but in chronic phase: 1\(^{83}\)
- A preliminary report: 1\(^{84}\)
- Not a report of a clinical trial: 1\(^{85}\)

Study Characteristics

The 10 studies selected\(^{28,86-94}\) were double-blind, randomized, and placebo-controlled clinical trials studying the effect of citicoline on the recovery of patients with acute ischemic stroke (Table 1). The oldest study was published in 1980 and the most recent study was published in 2012; thus, there is a gap of 32 years between the first and the last studies.
The included studies involved 4436 patients, but the number of patients evaluated was 4420. All the patients were 18 years or older, suffering from an acute ischemic stroke and treated within a time window of between 8 hours and 14 days.

Four trials were single centered, whereas all the other trials were multicentered. The treatments tested were either citicoline, with doses ranging from 250 to 2000 mg daily, or placebo. The duration of the treatment ranged from 10 days to 6 weeks. Citicoline or placebo was administered intravenously in 4 studies, orally in another 4 studies, and both intravenously and orally in 2 studies.

Four of the included trials were performed in Europe, four studies were performed in the USA, one study was performed in Japan, and one study in Venezuela.

The primary end point was different among the trials, but all have information about independence as at least as secondary outcome, allowing patient independence to be evaluated in the efficacy of the intervention. The timing of outcome measures varies between 10 days and 12 weeks. Safety was evaluated in all of the studies.

Table 2 shows the methodological quality of the selected studies. One major difference between the trials is the standard of care applied. In the trials performed in the 1980s, the standard of care comprised the use of activators of cerebral metabolism (i.e., hydergine), cerebral vasodilators (i.e., papaverine), vitamins, and methods for reducing blood pressure. In some cases, patients were also treated with hypertonic solutions, adrenocorticotropic hormone, or corticosteroids. Many of these interventions are not valid today. During the 1990s, the studies were performed in the United States, and the standard of care was more homogeneous, including anticoagulants, antiplatelets, and the use of rtPA in a few cases (less than 13% of cases). The standard of care used in the study performed in Venezuela included the use of antiplatelets, calcium channel blockers, and vitamins. In the ICTUS trial, the standard of care included a very early and aggressive treatment (stroke code), with more than 80% of patients treated in SU and more than 46% of patients receiving rtPA. Other differences to consider among the trials are the therapeutic window, with 2 studies having a therapeutic window of more than 48 hours, including the baseline severity of the patients (Table 1).

Synthesis of the Results

The effect estimates and the confidence intervals are presented as a forest plot in Figure 2. All the results are reported directly, as obtained from the original publication.
### Table 1. Summary of the included studies evaluating the efficacy of citicoline in acute ischemic stroke

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of patients</th>
<th>Age (mean, range)</th>
<th>Baseline severity</th>
<th>Therapeutic window</th>
<th>Dose</th>
<th>Route</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boudouresques and Michel</td>
<td>86</td>
<td>52 63.6</td>
<td>Mild–moderate</td>
<td>48 h</td>
<td>750 mg/day/10 days i.v.</td>
<td></td>
<td>10 days</td>
</tr>
<tr>
<td>Goas et al</td>
<td>87</td>
<td>64 62.8</td>
<td>Mild–moderate</td>
<td>48 h</td>
<td>250-750 mg/d/20 days i.v.</td>
<td></td>
<td>90 days</td>
</tr>
<tr>
<td>Corso et al</td>
<td>88</td>
<td>33 71.5</td>
<td>Mild–moderate</td>
<td>7-10 days</td>
<td>1 g/day/30 days i.v.</td>
<td></td>
<td>30 days</td>
</tr>
<tr>
<td>Tazaki et al</td>
<td>89</td>
<td>272 29-90</td>
<td>Mild–moderate</td>
<td>14 days</td>
<td>1 g/day/14 days i.v.</td>
<td></td>
<td>14 days</td>
</tr>
<tr>
<td>Clark et al (USA1)</td>
<td>86</td>
<td>259 67.8</td>
<td>NIHSS score higher than 4</td>
<td>24 h</td>
<td>500-2000 mg/day/6 weeks p.o.</td>
<td></td>
<td>12 weeks</td>
</tr>
<tr>
<td>Clark et al (USA2)</td>
<td>87</td>
<td>394 70.5</td>
<td>NIHSS score higher than 4</td>
<td>24 h</td>
<td>500 mg/day/6 weeks p.o.</td>
<td></td>
<td>12 weeks</td>
</tr>
<tr>
<td>Warach et al (USA3)</td>
<td>89</td>
<td>100 70.3</td>
<td>NIHSS score higher than 4</td>
<td>24 h</td>
<td>500 mg/day/6 weeks p.o.</td>
<td></td>
<td>12 weeks</td>
</tr>
<tr>
<td>Clark et al (USA4)</td>
<td>87</td>
<td>899 67.5</td>
<td>NIHSS score higher than 7</td>
<td>24 h</td>
<td>2000 mg/day/6 weeks p.o.</td>
<td></td>
<td>12 weeks</td>
</tr>
<tr>
<td>Alviarez and Gonzalez</td>
<td>84</td>
<td>65 69.8</td>
<td>NIHSS score higher than 4</td>
<td>8 h</td>
<td>2000 mg/day/6 weeks i.v. (3 days) then p.o. 6 weeks</td>
<td></td>
<td>6 weeks</td>
</tr>
<tr>
<td>Dávalos et al (ICTUS)</td>
<td>86</td>
<td>2298 72.8</td>
<td>NIHSS score higher than 7</td>
<td>24 h</td>
<td>2000 mg/day/6 weeks i.v. (3 days) then p.o. 12 weeks</td>
<td></td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

Abbreviations: i.v., intravenous; NIHSS, National Institutes of Health Stroke Scale; p.o., oral.

### Table 2. Quality measures of randomized controlled trials included

<table>
<thead>
<tr>
<th>Trial</th>
<th>Classification</th>
<th>Method of randomization and concealment of allocation</th>
<th>RCT stopped early (attrition bias)</th>
<th>Patients blinded</th>
<th>Health care provider blinded</th>
<th>Data collectors blinded</th>
<th>Outcome assessors blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boudouresques and Michel</td>
<td>A</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Goas et al</td>
<td>A</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Corso et al</td>
<td>B</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tazaki et al</td>
<td>A</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clark et al (USA1)</td>
<td>A</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clark et al (USA2)</td>
<td>A</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Warach et al (USA3)</td>
<td>A</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clark et al (USA4)</td>
<td>A</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Alviarez and Gonzalez</td>
<td>B</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dávalos et al (ICTUS)</td>
<td>A</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviation: RCT, randomized clinical trial.
The administration of citicoline was associated with a significant higher rate of independence (mRS score of 0-2), independently of the method of evaluation used (OR 1.56, 95% CI = 1.12-2.16 under random effects; OR 1.20, 95% CI = 1.06-1.36 under fixed effects). As the estimates are similar, then we can consider that any small-study effect has little effect on the intervention effect estimate.

Heterogeneity across Studies
As expected, a significant level of heterogeneity across studies was identified ($I^2 = 72.1\%$; $\tau^2 = .149; P = .0002$), reflecting the time gap of 32 years between the studies included in the meta-analysis. To explore this heterogeneity, a funnel plot was drawn. The funnel plot in Figure 3 shows evidence of asymmetry, and this asymmetry reflects the progressive improvement of the standard of care (placebo group) over time. The cumulative meta-analysis presented in Figure 4 shows how the effect of the intervention decreases over time in parallel with expected improvements in the standard of care. There are substantial differences between the standard of care for acute ischemic stroke patients in the 1980s compared with the standard of care now. All the included trials were

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%−CI</th>
<th>W(fixed)</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boudouresques 1980</td>
<td>11</td>
<td>23</td>
<td>9.17</td>
<td>1.56</td>
<td>[1.73; 48.60]</td>
<td>0.2%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Goas 1980</td>
<td>16</td>
<td>31</td>
<td>3.33</td>
<td>1.20</td>
<td>[1.15; 9.65]</td>
<td>0.9%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Corso 1982</td>
<td>7</td>
<td>17</td>
<td>23.57</td>
<td>2.89</td>
<td>[1.73; 4.81]</td>
<td>4.0%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Tazaki 1988</td>
<td>68</td>
<td>136</td>
<td>2.89</td>
<td>1.35</td>
<td>[0.75; 2.44]</td>
<td>4.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td>USA 1 1997</td>
<td>80</td>
<td>193</td>
<td>2.89</td>
<td>1.35</td>
<td>[0.75; 2.44]</td>
<td>4.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td>USA 2 1999</td>
<td>116</td>
<td>266</td>
<td>2.89</td>
<td>1.35</td>
<td>[0.75; 2.44]</td>
<td>4.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td>USA 3 2000</td>
<td>116</td>
<td>266</td>
<td>2.89</td>
<td>1.35</td>
<td>[0.75; 2.44]</td>
<td>4.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td>USA 4 2001</td>
<td>116</td>
<td>266</td>
<td>2.89</td>
<td>1.35</td>
<td>[0.75; 2.44]</td>
<td>4.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Alviare 2007</td>
<td>13</td>
<td>29</td>
<td>1.62</td>
<td>1.20</td>
<td>[0.57; 4.66]</td>
<td>1.2%</td>
<td>6.4%</td>
</tr>
<tr>
<td>ICTUS 2012</td>
<td>329</td>
<td>1148</td>
<td>1.62</td>
<td>1.20</td>
<td>[0.57; 4.66]</td>
<td>1.2%</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

Fixed effect model 2348 2072
Random effects model 1.20 [1.06; 1.36] 100% ---
1.56 [1.12; 2.16] 100% ---

Figure 2. Effect estimates and confidence intervals of the intervention on the rates of independence (mRS score of 0-2 or equivalent) in comparison with the placebo. Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio.

Figure 3. Funnel plot showing evidence of asymmetry.
performed with the highest quality in their time, as all the studies were performed in qualified centers.

In the sensitivity analysis, we performed the same analysis excluding those patients treated with rtPA from the studies USA4 and ICTUS. For this analysis, heterogeneity was lower ($I^2 = 64.5\%$, $P = .004$), still reflecting the time gap between the studies, but showing the appropriateness of this additional analysis. The independence rate in patients treated with citicoline but who did not receive rtPA was higher (OR 1.63, 95% CI = 1.18-2.24 under random effects; OR 1.42, 95% CI = 1.22-1.66 under fixed effects) (Fig 5). Of the patients not treated with rtPA and beginning the highest dose of citicoline (2 g/day/6 weeks) within the first 24 hours after stroke onset (Fig 6), the analysis also shows a positive result, with an OR of 1.27 (95% CI = 1.05-1.53), and, in this case, heterogeneity was not significant ($I^2 = 29.1\%$, $\tau^2 = .0193$, $P = .2375$). Regarding safety, none of the studies detected any safety concerns related to the intervention.

**Discussion**

In recent years, several clinical trials were conducted to find effective therapies, but no convincing results have been obtained. Although the randomized clinical trial has become the gold standard of evidence, there are some concerns about its overvaluation. In the field of acute ischemic stroke trials, a substantial change in the design and conduct of the trials has been demonstrated, but this has been accompanied by a reduction in external validity (or generalizability) of the results. There is concern among clinicians that external validity is often poor, and

![Figure 4.](image-url)

Cumulative meta-analysis under random-effects (a) and fixed-effects (b) models showing the dilution of the effect of the intervention over time. Abbreviations: CI, confidence interval; OR, odds ratio.

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>95%−CI</th>
<th>W(fixed)</th>
<th>W(random)</th>
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<td>Adding Tazaki 1998 (k=4)</td>
<td>2.53 [1.70; 3.57]</td>
<td>2.53 [1.70; 3.57]</td>
<td>2.53 [1.70; 3.57]</td>
<td>2.53 [1.70; 3.57]</td>
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<tr>
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<td>1.80 [1.44; 2.26]</td>
<td>1.80 [1.44; 2.26]</td>
<td>1.80 [1.44; 2.26]</td>
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<td>Adding USA 2 1999 (k=6)</td>
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<td>1.76 [1.37; 2.27]</td>
<td>1.76 [1.37; 2.27]</td>
<td>1.76 [1.37; 2.27]</td>
</tr>
<tr>
<td>Adding ICTUS 2012 (k=10)</td>
<td>1.20 [1.06; 1.36]</td>
<td>1.20 [1.06; 1.36]</td>
<td>1.20 [1.06; 1.36]</td>
<td>1.20 [1.06; 1.36]</td>
</tr>
</tbody>
</table>

![Figure 5.](image-url)

Effect estimates and confidence intervals of the intervention on the rates of independence (mRS score of 0-2 or equivalent) in comparison with placebo in patients not treated with rtPA. Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio.
this has led to the underuse of effective treatments. In the most recent trials, the findings may only be applicable to SUs that are participating in clinical trials and may not be applicable in day-to-day clinical practice.100

The present systematic review and meta-analysis offer data on the effect of citicoline in the treatment of acute ischemic stroke in comparison with placebo. The studies included in the review are double-blind and placebo-controlled, and were conducted in academic centers. The studies are of the highest quality for the time they were performed. We tried to minimize as much as possible the risk of bias.95,101 We did not include 3 studies25,27 because only the abstracts of these studies were available (the studies were never published), so we could not verify the quality of the studies. It has to be considered that our estimates coincide with those reported in previous meta-analyses25,27 showing that the use of citicoline was associated with a decrease on the rates of long-term death and disability. Also, the results obtained in the FDA25 coincide with our results, showing how citicoline increased the rates of total recovery in patients with moderate to severe ischemic stroke.

By definition, a systematic review is a summary of the medical literature that uses explicit methods to perform a thorough literature search and critical appraisal of individual studies, and which also uses appropriate statistical techniques to combine these valid studies.102 It is reasonable to suggest that a systematic review should be performed (or updated) after each and every study in the development of a new intervention, and that doing so will enhance decision making when deciding whether to proceed with further development, as well as when implementing the positive findings for a new intervention.102,103 This process inevitably brings together studies that are diverse in their design, but it is incontrovertible that treatment decisions should be based on evidence when it exists and that good quality systematic reviews provide an essential mechanism in reviewing available evidence.104

As mentioned before, the major differences between the trials included in this systematic review are related with the changes of the standard for acute ischemic stroke treatment. This finding is relevant when we are trying to evaluate today the efficacy of a product that has been on the market for more than 35 years. Furthermore, the changes in the standard of care across time is a well-known source of heterogeneity.95,105 Thus, we have to consider that when an active treatment is given, the overall response is the result of the treatment itself and the context in which it is given.106

Following the results obtained in the ICTUS trial,28 the efficacy of citicoline could be questioned, but we have to consider the poor external validity of the trial. In fact, the lesson we learnt with the ICTUS trial is that, in the case of a patient treated very early with rtPA in a multidisciplinary SU, citicoline is not able to provide any additional beneficial effect. This can be considered the gold standard for the treatment of acute ischemic stroke but differs very much from actual clinical practice in the world.95,107

Another point to consider is the controversy in recruiting rtPA-treated patients in stroke trials,108 as we cannot rule out a ceiling effect resulting from an already maximal improvement due to rtPA use. This fact has been argued as a possible explanation for the failure of some recent acute ischemic stroke trials.28,109,110 One argument in favor of this hypothesis is the higher odds obtained in our sensitivity analysis, which includes only patients not treated with rtPA.

We investigated the source of heterogeneity among the trials included in this review and we considered that the explanation of this heterogeneity was the difference in the standard of care for patients, rather than the quality of the studies. This effect is evaluable in the cumulative meta-analysis. Thus, our conclusion that the effect of
citicoline could be diluted over time in parallel with progressive improvements in the standard of care for acute ischemic stroke patients appears to be valid. The analysis performed with more recent studies (Fig 6), in patients who received the highest dose of citicoline in the first 24 hours without rtPA treatment, should be considered the real size of the effect of citicoline in a more contemporary context. This could help in defining what kind of patients could benefit from treatment with citicoline. Further advantages of citicoline include the long time window compared to rtPA and the administration of the treatment not only in well-staffed, well-trained, and well-equipped stroke services administering thrombolysis but also in much less advanced stroke services.

It can be concluded that the current systematic review and meta-analysis support some benefits of citicoline in the treatment of acute ischemic stroke. It is confirmed that the effect of citicoline has been diluted over time in parallel with improvements in the standard of care. Consequently, on top of the best treatment available (rtPA), citicoline offers a limited benefit.

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