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Rationale for the Use of Citicoline in the Management of Brain Ischemia Related Disorders

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Citicoline is a drug available in several countries worldwide. Among the European Union countries, citicoline is registered as a Rx product in France, Italy, Spain, Bulgaria and Portugal. It's also registered as a drug in other important countries out of Europe (Russia, Mexico, Japan, Brazil, India, Algeria, Argentina, Egypt, etc), being present up to 80 countries as a Prescription Medicine.

The main indications of the use of citicoline are:

1. Acute ischemic stroke and its sequelae
2. Traumatic brain injury (TBI) and its sequelae

For these diseases citicoline combine neurovascular protection and repair effects. Citicoline acts at several levels of the ischemic cascade and a series of brain repair effects have been reported [1]. Citicoline has been extensively studied in clinical trials with over 11 000 patients and volunteers who have various neurological disorders, including acute ischemic stroke [2-10]. In all these studies, citicoline had a similar safety profile as compared with placebo [2]. In a pooled analysis with individual patient data of randomised clinical trials, with an odds ratio of 0.64 (95% CI 0.54-0.72). And these effects are cost-effective [13,14]. Three years ago, the results of the ICTUS trial, made in Europe were published [15], with an overall neutral result because the circumstances of the study (46% patients treated with rtPA, median NIHSS 15 and bigger infarcts not excluded), concluding that on top of the best treatment possible, citicoline does not show any clinical improvement but, as shown in the updated fixed-effects meta-analysis, the effect of the drug remains significant (OR 1.14, 95% CI 1.00–1.30). A complete and updated meta-analysis presented in the final report of the trial, demonstrates that the effect of citicoline on acute and subacutestroke patients has an OR of 1.22 (95% CI 1.07–1.38), with the fixed-effects model, or an OR of 1.60 (95% CI 1.17–2.20) with the random-effect model [16]. Recently, a new meta-analysis based on acute and subacute ischemic stroke (Figure 1) demonstrates the efficacy of citicoline on this indication, with an OR of 1.56 (95%CI, 1.12;2.16) [17], and also demonstrates that the effect is more evident I no-rTPA treated patients.

For the sequelar phase, the efficacy of the drug is based on a Cochrane Systematic Review [18] based in 14 Placebo-Controlled, by

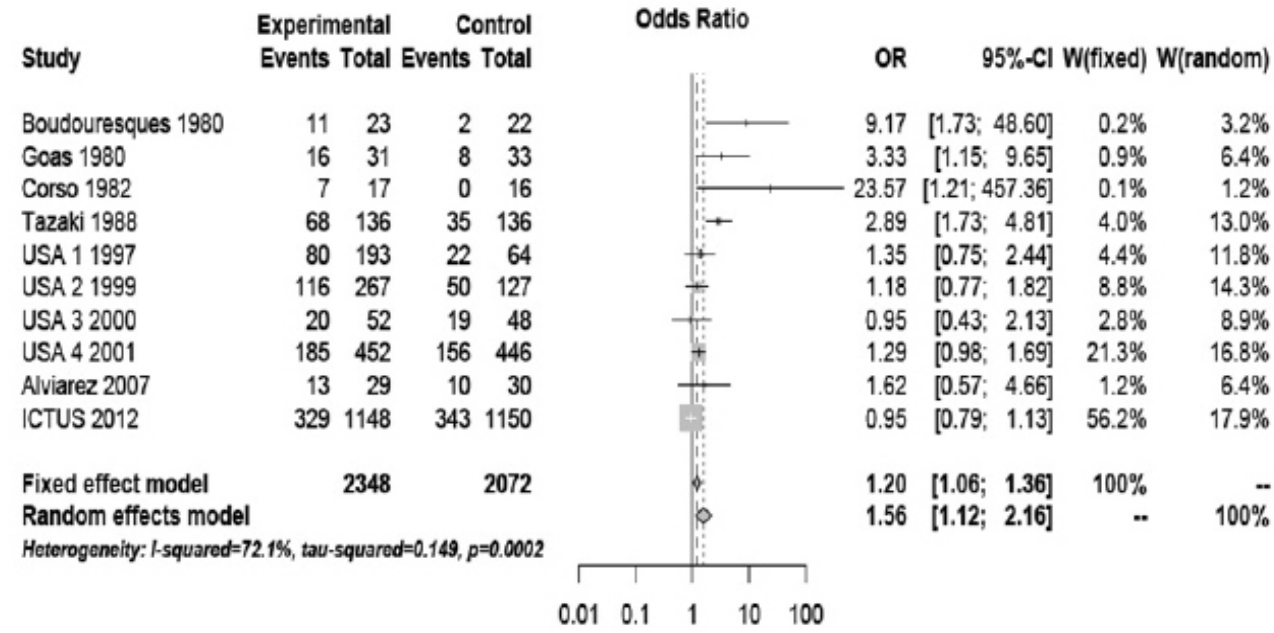

Figure 1: Effect estimates and confidence intervals of the intervention on the rates of independence (mRS=0-2 or equivalent) in comparison with placebo in acute ischemic stroke patients. OR 1.56 (95% CI=1.12;2.16).

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Randomized Clinical Trials qualified as "Highest Quality Trials (A)" by The Cochrane Collaboration in which was demonstrated that citicoline has a positive effect on memory and behaviour, especially in patients with chronic cerebrovascular diseases. It also was demonstrated in the Cochrane Review that Clinical Global Impression was also improved by Citicoline. Recently, these data have been confirmed in two new studies, in which the authors concluded that citicoline treatment for 12 months in patients with first-everischemic stroke is safe and probably effective in improving post-stroke cognitive decline, thus citicoline appears to be a promising agent to improve recovery after stroke [19]. In the IDEALE study it was demonstrated that citicoline maintained the cognitive score on MMSE in patients diagnosed with Mild vascular Cognitive Impairment [21]. There is evidence also of a positive effect of citicoline on the recovery of motor sequelae after stroke when added to rehabilitation programs (Figure 2)[21].

Regarding the efficacy in TBI, the evidence of efficacy is provided by several trials collected in many reviews 2 and in a new published meta-analysis based on all comparative trials of citicoline (Figure 3) [22], with also positive data on the treatment of neuropsychological deficits after TBI [23].

Competing Interests

The authors have no competing interests with the work presented in this manuscript.

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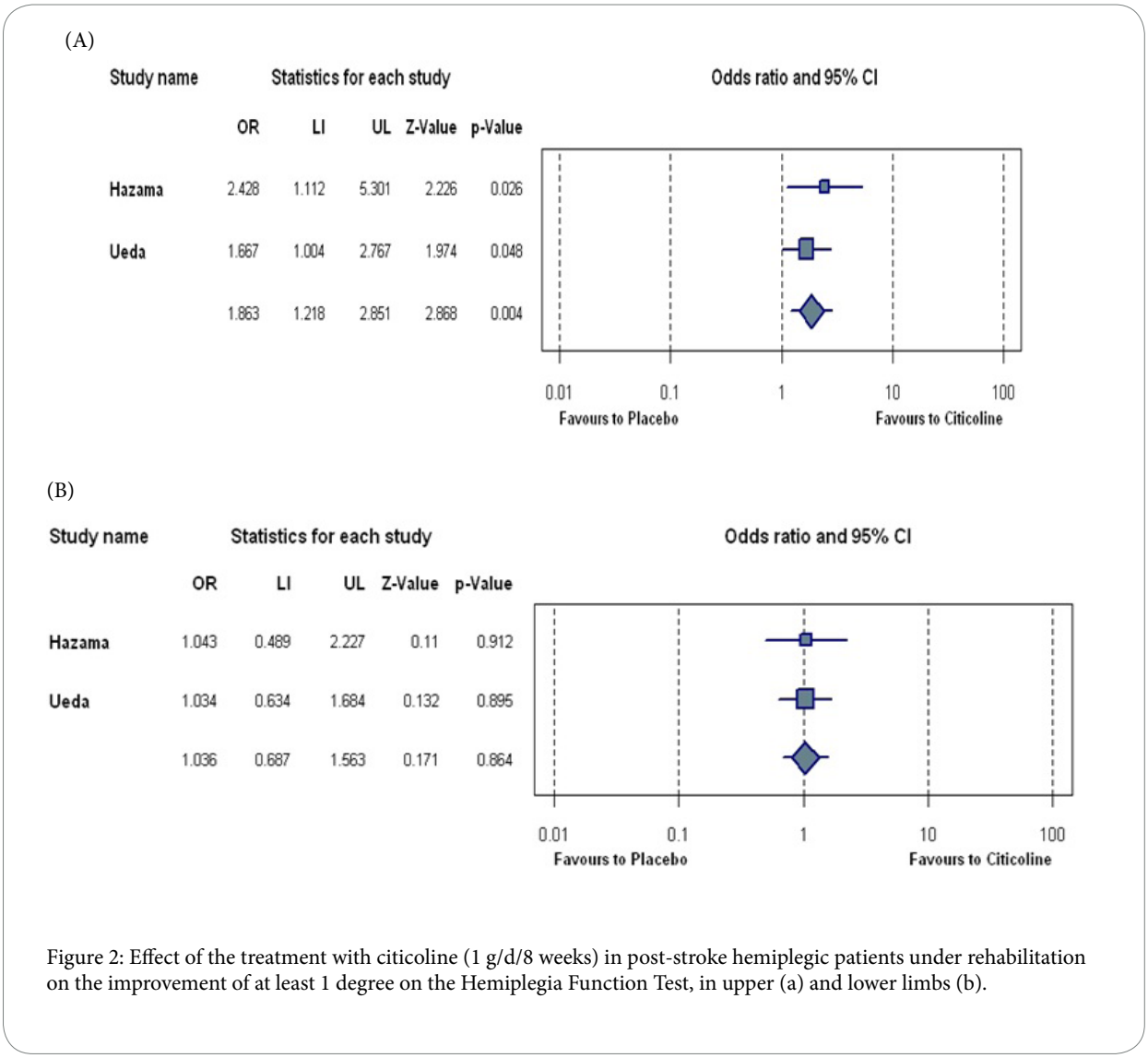

Figure 2: Effect of the treatment with citicoline (1 g/d/8 weeks) in post-stroke hemiplegic patients under rehabilitation on the improvement of at least 1 degree on the Hemiplegia Function Test, in upper (a) and lower limbs (b).

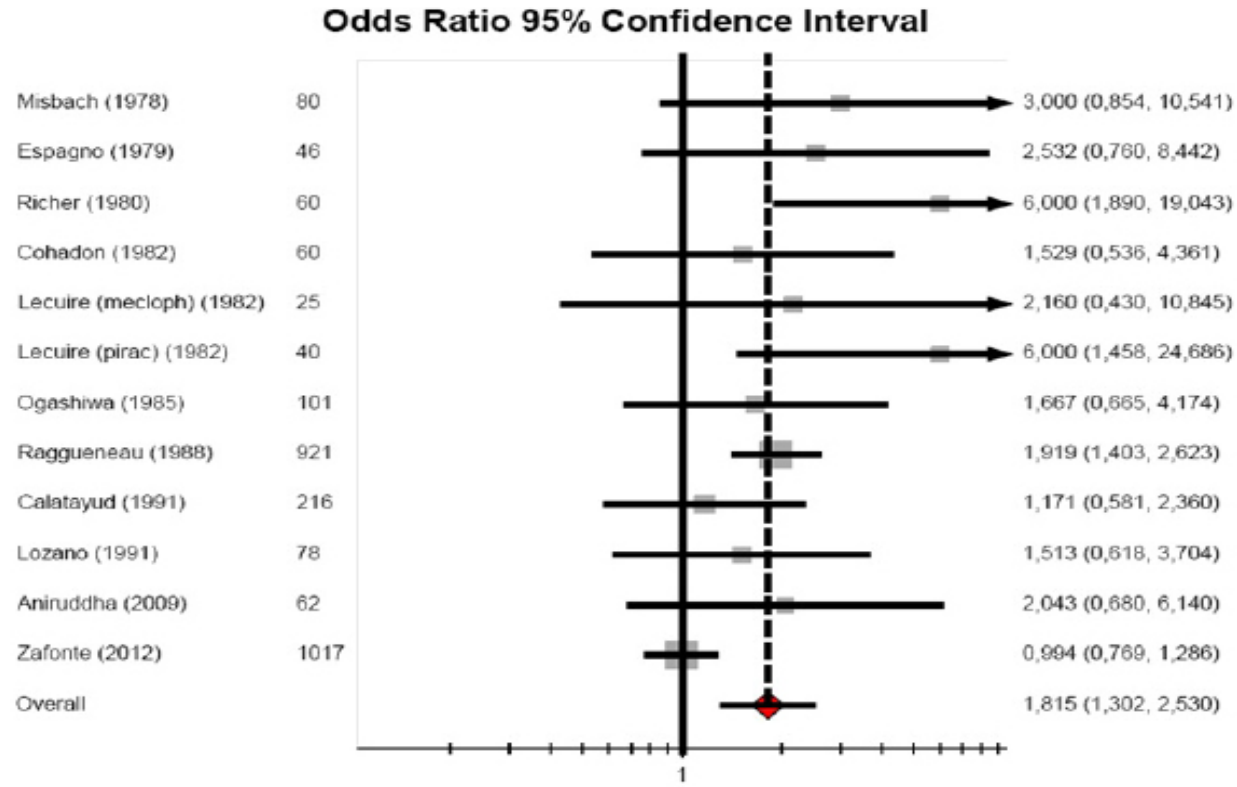

Figure 3: Forest Plot of the meta-analysis on TBI based on the random-effects model. OR 1.815 (95% CI=1.302;2.530).

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