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File: ■ Ginkgo (*Ginkgo biloba*)
■ Acute Ischemic Stroke
■ Neuroprotection

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RE: Ginkgo Improves Outcomes in Patients following Acute Ischemic Stroke

Oskouei DS, Rikhtegar R, Hashemilar M, et al. The effect of *Ginkgo biloba* on functional outcome of patients with acute ischemic stroke: a double-blind, placebo-controlled, randomized clinical trial. *J Stroke Cerebrovasc Dis*. November 2013;22(8):e557-e563.

Acute ischemic stroke (AIS) accounts for 88% of stroke events. During AIS, neurons die in part due to oxidative stress. Preclinical studies show that ginkgo (*Ginkgo biloba*) provides neuroprotection. Clinical studies are needed to evaluate the effect of ginkgo in the management of AIS. The purpose of this prospective, randomized, placebo-controlled clinical trial was to assess the effect of ginkgo on functional outcomes of patients with AIS.

Consecutive patients (n = 102) with AIS involving the anterior cerebral circulation, who were ≥ 45 years old, and admitted to Tabriz Imam Reza and Razi Hospitals, East Azerbaijan province, Iran, between January 2009 and September 2011 were included in this study. The exclusion criteria were as follows: anticoagulant therapy; patients with chronic kidney, hepatic, and hematologic diseases; pregnant or lactating women; and having a profound loss of consciousness (i.e., stupor and coma). Only patients with involvement of the anterior circulation were included, because patients with posterior circulation insufficiency receive anticoagulation agents which should not be used simultaneously with ginkgo. For 4 months, patients received either placebo or 120 mg/day ginkgo (Gol-Darou Company; Isfahan, Iran). The clinical severity and functional ability of patients were assessed with the National Institutes of Health Stroke Scale (NIHSS). The primary outcome measure was a 50% reduction in the 4-month NIHSS score compared with baseline. Blood was drawn to measure fasting blood glucose, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, triglyceride, prothrombin time, international normalized ratio, and partial thromboplastin time at admission.

There were no significant differences between age and sex distribution or for any of the biochemical or hematological parameters. Both treatment groups had a similar mean difference in NIHSS score between baseline and 4-month follow-up, and between baseline and hospital discharge. A total of 58.6% of ginkgo-treated patients had a 50%

improvement in outcomes, statistically significant compared with 18.5% of placebo-treated patients ($P < 0.05$). A total of 81.6% of ginkgo-treated patients had ≥ 1 stage improvement in stroke severity (i.e., from moderate to mild), and 68.8% of placebo-treated patients had ≥ 1 stage improvement in stroke severity, a difference that was not statistically significant ($P > 0.05$). When adjusting for age and gender, there was a significant improvement in NIHSS scores in the ginkgo group compared with the placebo group ($P < 0.05$). Adverse events were not reported.

The authors conclude that ginkgo can improve functional recovery in patients with AIS, and ginkgo may be providing neuroprotection. The authors state that ginkgo should be recommended after AIS; although they acknowledge that additional research is needed to confirm the findings. Of note, a higher daily dose (e.g., 240 mg) might be more effective, as in the treatment of cognitive impairment and dementia. Treatment for patients with AIS is limited because most pharmaceuticals must be administered as soon as possible for the most robust effect. The authors did not discuss the data in relation to when treatment was initiated. It would be interesting and of medical value to determine whether ginkgo was effective after a delay in seeking treatment. An important limitation of the study is that the authors did not discuss time of treatment initiation. For the placebo group to be a true control, both groups would need to have a similar time of treatment initiation. In addition, aside from noting the manufacturer that produced the 40 mg ginkgo tablets, the preparation was not characterized regarding its processing or content.

—Heather S. Oliff, PhD

Peer Review Comment:
There are some quality of reporting issues with this paper. It is not stated who carried out the randomization procedure, whether the analysis was per protocol or intention-to-treat, or if any check on blinding was carried out at the end of the study (i.e., asking patients if they thought they had received placebo or verum). The authors could have used the CONSORT (Consolidated Standards of Reporting Trials) herbal guidelines as a basis for reporting details of the herbal intervention as well as the standard CONSORT statement for reporting of randomized, controlled trials (RCTs) in general. It is quite remarkable that this paper does not discuss monitoring of, or provide any data on, adverse events. Since the authors state that "*G. biloba* is recommended after AIS," some consideration of safety aspects, including any potential for interactions with conventional medicines used, should have been included.

A related point about quality of reporting of this trial with respect to the "herbal" elements is that ginkgo is frequently misspelt in the paper (as Gingko), including in the keywords.

The American Botanical Council has chosen not to include the original article.