# Folic acid supplementation among adults with hypertension reduces risk of stroke

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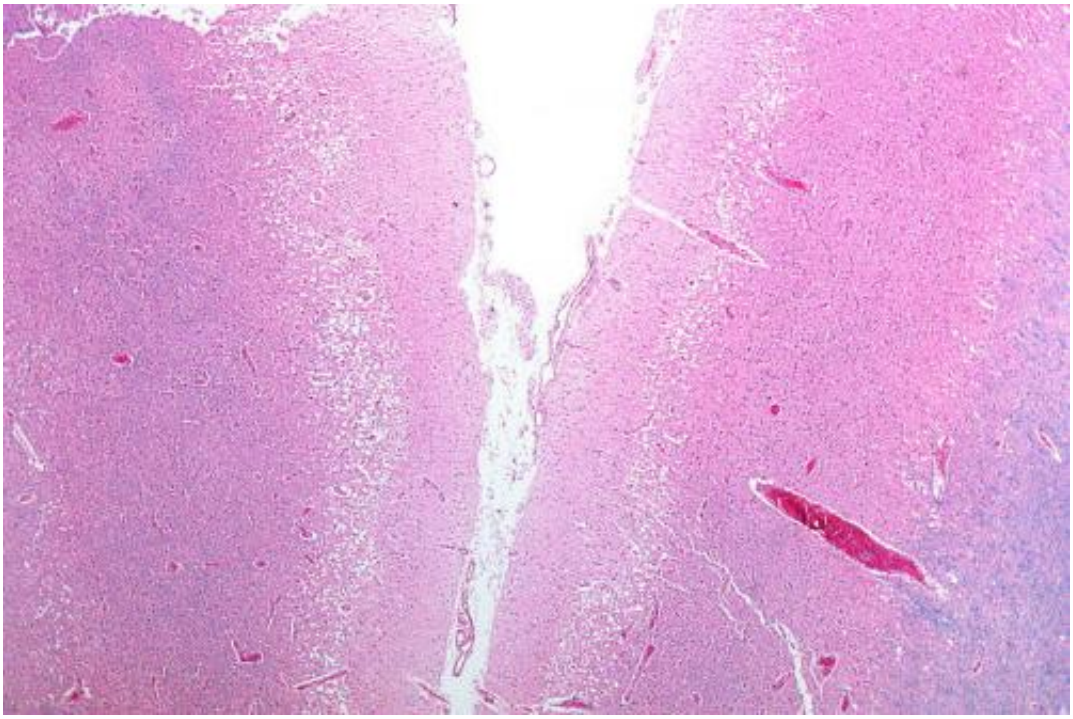

Micrograph showing cortical pseudolaminar necrosis, a finding seen in strokes on medical imaging and at autopsy. H&E-LFB stain. Credit: Nephron/Wikipedia

In a study that included more than 20,000 adults in China with high blood pressure but without a history of stroke or heart attack, the combined use of the hypertension medication enalapril and folic acid, compared with enalapril alone, significantly reduced the risk of first stroke, according to a study appearing in *JAMA*. The study is being

released to coincide with its presentation at the American College of Cardiology Annual Scientific Session.

Stroke is the leading cause of death in China and second leading cause of death in the world. Primary prevention (prevention prior to a first episode) is particularly important because about 77 percent of strokes are first events. Uncertainty remains regarding the efficacy of folic acid therapy for primary prevention of stroke because of limited and inconsistent data, according to background information in the article.

Yong Huo, M.D., of Peking University First Hospital, Beijing, China, and colleagues had 20,702 adults with hypertension without history of stroke or heart attack randomly assigned to receive daily treatment with a single-pill combination containing enalapril (10 mg) and folic acid (0.8 mg; n = 10,348), or a tablet containing enalapril alone (10 mg; n = 10,354). The trial was conducted from May 2008 to August 2013 in 32 communities in Jiangsu and Anhui provinces in China. Participants were tested for variations in the MTHFR C677T gene (CC, CT, and TT genotypes) that may affect folate levels.

During a median treatment duration of 4.5 years, first stroke occurred in 282 participants (2.7 percent) in the enalapril-folic acid group compared with 355 participants (3.4 percent) in the enalapril group, representing an absolute risk reduction of 0.7 percent and a relative risk reduction of 21 percent. Analyses also showed significant reductions among participants in the enalapril-folic acid group in the risk of ischemic stroke (2.2 percent vs 2.8 percent) and composite cardiovascular events (cardiovascular death, heart attack and stroke) (3.1 percent vs 3.9 percent).

There was no significant difference between groups in the risk of hemorrhagic stroke, heart attack, or all-cause death, or in the frequencies of adverse events.

The authors write that this trial (China Stroke Primary Prevention Trial; CSPPT), with data on individual baseline folate levels and MTHFR genotypes, has provided convincing evidence that baseline folate level is an important determinant of efficacy of folic acid therapy in stroke prevention. "The CSPPT is the first large-scale randomized trial to test the hypothesis using individual measures of baseline folate levels. In this population without folic acid fortification, we observed considerable individual variation in plasma folate levels and clearly showed that the beneficial effect appeared to be more pronounced in participants with lower folate levels."

"We speculate that even in countries with folic acid fortification and widespread use of folic acid supplements such as in the United States and Canada, there may still be room to further reduce stroke incidence using more targeted folic acid therapy—in particular, among those with the TT genotype and low or moderate folate levels."

"The trial by Huo et al has important implications for stroke prevention worldwide," write Meir Stampfer, M.D., Dr.P.H., and Walter Willett, M.D., Dr.P.H., of the Harvard T. H. Chan School of Public Health and Channing Division of Network Medicine, Boston, in an accompanying editorial.

"Although the trial participants all had hypertension, there is little reason to doubt that the results would apply to normotensive persons, although the absolute effect would be smaller. It is possible to debate the ethics of whether a replication trial should be performed, especially because folic acid supplementation (or fortification) is safe and inexpensive, and carries other benefits. Large segments of the world's population, potentially billions of people, including those living in northern China, Bangladesh, and Scandinavia, have low levels of folate."

"Individuals with the TT genotype might particularly benefit, although it

seems unlikely that genotyping for that purpose would be cost-effective. Also, some persons in the United States on the low end of the distribution of folate intake may benefit; effects in this subgroup would not have been detected in previous trials. Ideally, adequate folate levels would be achieved from food sources such as vegetables (especially dark green leafy vegetables), fruits and fruit juices, nuts, beans, and peas. However, for many populations, achieving adequate levels from diet alone is difficult because of expense or availability. This study seems to support fortification programs where feasible, and supplementation should be considered where fortification will take more time to implement."

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