

# ACC: Folate Supplements Cut Strokes in Hypertension

— Hypertensive patients with low blood folate levels gain big benefit.

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SAN DIEGO -- Folic acid supplements significantly decreased risk of first stroke in those with hypertension, results of a Chinese trial showed.

In a randomized trial of more than 20,000 participants with hypertension, 2.7% of those taking folic acid along with the blood pressure drug enalapril (Vasotec) experienced first strokes, compared with 3.4% of those taking enalapril alone (hazard ratio 0.79, 95% CI 0.68-0.93;  $P=0.003$ ). The results were published in the *Journal of the American Medical Association* on March 15.

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folate acid fortification, including in Asia and other countries," wrote the authors, who were led by [Yong Huo, MD](#), at the Peking University First Hospital in Beijing, China. "This finding is consistent with a benefit from folate use among adults with hypertension and low baseline folate levels."

Participants, all from the China Stroke Primary Prevention Trial (CSPPT), were treated with 10 milligrams of enalapril in the control group, or with 0.8 mg of folic acid and enalapril in the intervention group. They were treated for a median of 4.5 years, from 2008 to 2013, and were an average age of 60. None of the patients had a history of strokes or myocardial infarction.

The participants were also separated by methylenetetrahydrofolate (*MTHFR*) *C677T* genotype because of previous research suggesting that the *C677T* gene might be responsive to folate status.

"One of the really interesting parts of this study is that they stratified the analyses by the genotype of the participants," said [Sylvia Wassertheil-Smoller, PhD](#), a professor at the Albert Einstein College of Medicine, who was not affiliated with the study. "It's a very important development, because we're always hearing about personalized medicine, and this is an attempt to further that line of research."

The frequency of the *MTHFR* polymorphism was 27.3% for the CC genotype (normal homozygous,  $n=5,562$ ), 49.2% for CT (heterozygous variant,  $n=10,176$ ), and 23.5% for TT (homozygous variant,  $n=4,874$ ). For participants with the CC genotype with folate levels below the median, the intervention reduced the risk of stroke (HR 0.45, 95% CI 0.29-0.72,  $P=0.001$ ).

"A similar pattern was observed to a lesser degree among those with the CT genotype, with the greatest benefit seen in the lowest quartile (absolute RR 1.4%, HR 0.6; 95% CI 0.44-1.07,  $P=0.10$ )," wrote Huo and colleagues. "In contrast, among those with the TT genotype, the preventive effect of folic acid therapy on stroke was mainly observed in the highest folate quartile (absolute reduction 2.8%, HR 0.24; 95% CI 0.10-0.58,  $P=0.001$ )."

Participants with the TT genotype had the highest risk of stroke. "This finding underscores the basic principle that for trials of nutrients, in contrast to most drug trials, the baseline levels are critical to consider, and targeting individuals with low levels of the nutrient under study provides the best test of the hypothesis," wrote [Meir Stampfer, MD](#), and [Walter Willett, MD](#), both of the Harvard TH Chan School of Public Health in Boston [in an accompanying editorial](#).

They also wrote that the trial has implications for stroke prevention worldwide.

"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," they noted. "Individuals with the TT genotype might particularly benefit, although it seems unlikely that genotyping for that purpose would be cost-effective."

Significant risk reductions were also found for first ischemic stroke (2.2% versus 2.8% for the control group; HR 0.76, 95% CI 0.64-0.91), and composite cardiovascular events of cardiovascular death, myocardial infarction (MI), and stroke (3.1% versus 3.9%; HR 0.80, 95% CI 0.69-0.92).

But hemorrhagic stroke and all-cause mortality did not differ significantly across the two main groups. The majority of participants took at least 70% of their medications throughout the trial. The discontinuation rate for both groups was around 14%.

Folate levels increased by a median of 11.2 ng/mL in the intervention group and 4.4 ng/mL in the control group. Levels did not differ by genotype. Both groups had comparable blood pressure levels at baseline -- 129.8/83.1 mm Hg in the folic group versus 139.8/83.1 mm Hg in the enalapril only group. The number needed to treat to prevent one stroke was 141, for 4.5 years.

Limitations of the study included its fixed dosage of folic acid. The optimal dosage for those with the *MTHFR* genotype and for those with certain baseline folate levels remains unknown. The findings may not be generalizable, especially to adults without hypertension. In addition, the trial was designed mostly for its primary endpoint and is "underpowered for assessing some secondary outcomes, particularly hemorrhagic stroke, MI, and total mortality," noted the authors.

Stampfer and Willett wrote that these "remarkable findings" may underestimate the effect of folic acid therapy because adherence was imperfect and folate levels increased substantially even in the control group in the trial. In addition, the trial was stopped early for ethical reasons, and a more robust effect could have been seen if it was carried through.

**Researchers disclosed no relevant relationships with industry.**

#### **Primary Source**

*Journal of the American Medical Association*

Source Reference: [Huo M, et al "Efficacy of folic acid therapy in primary prevention of Stroke among adults with hypertension in China: The CSPPT randomized clinical trial" JAMA 2015; DOI: 10.1001/jama.2015.2274](#)

#### **Secondary Source**

*Journal of the American Medical Association*

Source Reference: [Stampfer, M and Willet, W "Folate supplements for stroke prevention: Targeted trial trumps the rest" JAMA 2015; DOI: 10.1001/jama.2015.1961](#)

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