EDITORIAL

Folate Supplements for Stroke Prevention
Targeted Trial Trumps the Rest

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The effect of folate supplementation on cardiovascular disease has been studied in many observational studies and randomized trials and has been a topic of debate for a number of years. In this issue of *JAMA*, Huo and colleagues[1] provide results from their important clinical trial of folic acid therapy for primary prevention of stroke. In a carefully designed and executed randomized trial, 20 702 adults with hypertension were randomized to receive enalapril alone (n = 10 354) or enalapril combined with 0.8 mg folic acid (n = 10 348). As recommended by the data and safety monitoring board, the trial was terminated early, after 4.5 years, with emergence of a significant reduction in the incidence of first stroke, the primary end point, of 2.7% (282 events) in the enalapril-folic acid group vs 3.4% (355 events) in the enalapril alone group (hazard ratio, 0.79; 95% CI, 0.68-0.93). In further support of the finding, the benefit was more pronounced in the prespecified subgroup of study participants with the lowest baseline levels of plasma folate (ie, <5.6 ng/mL) with rates of first stroke of 2.8% (73 events among 2600 participants) in the enalapril-folic acid group vs 4.6% (116 events among 2548 participants) in the enalapril alone group (hazard ratio, 0.61; 95% CI, 0.45-0.82). There was a smaller effect among those in higher baseline folate categories.

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These remarkable findings may represent an underestimate of the potential true effect of folic acid supplementation in this setting for several reasons. First, adherence was imperfect, although high. Approximately 69% of participants took at least 70% of their assigned pills overall. Second, mean folate levels in the control group increased substantially—by 60% during the course of the trial, with an especially marked increase among those with the lowest levels at baseline. The cause of this increase is unclear—whether due to improvements in diet or use of supplements in the control group. Either way, this change and the incomplete adherence diminished the contrast between the groups and likely attenuated the apparent benefit. Third, for ethical reasons the trial was stopped early, and the full effects may take longer to be seen; indeed, there was a suggestion of increasing benefit in the treatment group vs the control group over time.

This trial by Huo et al provides important lessons for the design and interpretation of results from randomized trials and carries broad implications for stroke prevention worldwide. The possible benefits of folic acid supplementation for cardiovascular disease have been controversial. Early observational studies suggesting a link between low folate and risk of cardiovascular disease[2-5] stimulated the initiation of randomized trials, mostly conducted among patients who already had experienced a cardiovascular event. Most of the trials have yielded null results.[6] Attempts to reconcile the apparently divergent results based on trial design and differences in baseline folate levels were largely dismissed.[7]

Also, initial Mendelian randomization studies relating the methylenetetrahydrofolate reductase (*MTHFR*) C677T mutation to cardiovascular outcomes also appeared to be null.[8] MTHFR is a major regulatory enzyme for folate metabolism, and the TT genotype has reduced enzyme activity and, hence, lower circulating levels of folate. If folate is related to cardiovascular disease, individuals with the TT genotype would be expected to be at higher risk, so the apparently null findings tended to argue against an effect of folate.

However, the hypothesis was not abandoned. Recognition has increased that any effect of supplementation would primarily benefit those with insufficient levels at baseline. In countries such as the United States with folate fortification of grain products (implemented to reduce incidence of neural tube defects), the proportion of individuals with very low folate levels has decreased substantially. In a 1999 report from the Framingham cohort, mean folate levels increased from 4.6 ng/mL to 10.0 ng/mL after fortification, and the proportion of study participants with levels less than 3 ng/mL decreased from 22% to 1.7%.[9] In the US VISP trial of B vitamin supplementation in a poststroke setting, which was null, mean baseline levels of folate were 12.4 ng/mL compared with 8.1 ng/mL in the present trial by Huo et al. This concept of interaction by baseline folate status was further supported by an extension of the *MTHFR* Mendelian randomization analysis, which found that significant findings were limited to study participants living in regions with low folate levels.[10] For example, in the current trial, those with the TT genotype had higher stroke rates. 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.

A second lesson is the importance of precise targeting of the end points. Prior observational studies and trials suggested that the greatest benefit from folate might be for stroke, which was the designated primary end point in the current trial. In a previous meta-analysis of randomized trials, Huo et al found that folic acid supplements were associated with a significantly reduced stroke risk (relative risk, 0.92), particularly

in regions with incomplete or no fortification (relative risk, 0.89).[11] Also, most of the previous trials had been conducted among individuals with prior cardiovascular disease. Such trials address important questions for treatment of such patients and are appealing because trials in high-risk participants tend to require a smaller sample size. However, null results cannot automatically be generalized to the primary prevention setting, in part because patients may be treated with an array of other medications that could obscure any benefit of intervention for primary prevention. Another important difference between this trial and other trials was the background of other preventive measures. In contrast to most previous trials, in this trial, less than 1% of the participants were taking lipid-lowering therapy and less than 3% were taking antiplatelet agents.

The trial by Huo et al has important implications for stroke prevention worldwide. Although the trial participants all had hypertension, it is likely 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.[12] 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.

ARTICLE INFORMATION

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