

Platelet Count Affects Efficacy of Folic Acid in Preventing First Stroke



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ABSTRACT

BACKGROUND The role of platelets and important effect modifiers on the risk of first stroke is unknown.

OBJECTIVES This study examined whether low platelet count (PLT) and elevated total homocysteine (tHcy) levels jointly increase the risk of first stroke, and, if so, whether folic acid treatment is particularly effective in stroke prevention in such a setting.

METHODS A total of 10,789 Chinese hypertensive adults (mean age 59.5 years; 38% male, with no history of stroke and myocardial infarction) were analyzed from the China Stroke Primary Prevention Trial, where participants were randomly assigned to daily treatments of 10 mg enalapril and 0.8 mg folic acid (n = 5,408) or 10 mg enalapril alone (n = 5,381). The primary endpoint was first stroke.

RESULTS During 4.2 years of follow-up, a total of 371 first strokes occurred. In the enalapril-alone group, the lowest rate of first stroke (3.3%) was found in patients with high PLT (quartiles 2 to 4) and low tHcy (<15 μmol/l); and the highest rate (5.6%) was in patients with low PLT (quartile 1) and high tHcy (≥15 μmol/l) levels. Following folic acid treatment, the high-risk group had a 73% reduction in stroke (hazard ratio: 0.27; 95% confidence interval: 0.11 to 0.64; p = 0.003), whereas there was no significant effect among the low-risk group.

CONCLUSIONS Among Chinese hypertensive adults, the subgroup with low PLT and high tHcy had the highest risk of first stroke, and this risk was reduced by 73% with folic acid treatment. If confirmed, PLT and tHcy could serve as biomarkers to identify high-risk individuals who would particularly benefit from folic acid treatment. (China Stroke Primary Prevention Trial [CSPPT]; [NCT00794885](https://doi.org/10.1186/1745-6215-13-1)) (J Am Coll Cardiol 2018;71:2136–46) © 2018 by the American College of Cardiology Foundation.

Stroke is the second leading cause of death in the world (1). It is the number 1 cause of death in China, and the number 4 cause of death in the United States (2,3). Globally, there is an urgent need to develop safe, inexpensive, and effective primary prevention strategies for stroke to halt or reverse the rapidly rising trend of stroke in China

and many other developing countries (4), given that about 77% of strokes are first events (5,6).

Platelets play an important role in the pathogenesis of vascular disease (7). Previous relevant studies have examined the role of platelets in the acute phase of stroke (8,9). Only 1 prospective study has investigated the relationship between platelets and risk of



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incident stroke (10), and no studies have examined the association of platelet count (PLT) with first stroke.

A recognized mechanism by which platelets contribute to the development of atherosclerosis is by interacting with endothelium or connective tissue secondary to endothelial injury. In the normal physiological state, endothelial cells can inhibit platelet adherence by their capacity to produce antithrombotic substances (e.g., prostacyclin and heparin) (11). It is possible that various forms of endothelial injury may promote platelet adherence and the release of platelet constituents, as in, for example, the presence of elevated total homocysteine (tHcy) (12,13). As such, low PLT could be a marker of endothelial injury and platelet adherence.

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Elevated tHcy is a known risk factor of endothelium injury, atherosclerosis, and cardiovascular disease (13–16). In animal models, experimental homocysteinemia in baboons caused a spectrum of endothelial injury, ranging from alterations in cell-surface constituents to increased turnover (non-denuding injury) or, after extreme injury, loss of endothelial cover (17). The atherogenic mechanism of homocysteinemia has been demonstrated in a primate model by measuring endothelial cell loss and regeneration, platelet consumption, and intimal lesion formation (18). It is conceivable that platelets and tHcy may enhance each other, thereby jointly affecting an individual's risk of stroke. However, to date, there are no adequately powered prospective studies to examine the joint association of PLT and elevated tHcy with the risk of first stroke.

From the standpoint of primary prevention of stroke, there is considerable interest as to whether folic acid (a synthetic form of folate, an essential B vitamin) supplementation can effectively reduce the risk of stroke among those individuals characterized by low PLT and high tHcy levels, particularly among populations residing in regions with low folate intake and without mandatory folic acid fortification of grain products. This interest was heightened by the main

finding of the CSPPT (China Stroke Primary Prevention Trial), which showed that folic acid treatment could reduce the risk of first stroke by 21% in hypertensive men and women (19). Given that folic acid can effectively lower tHcy, can improve endothelial function, and has antioxidant properties, it is biologically plausible that folic acid treatment may be particularly effective under the conditions of low PLT and high tHcy (20,21).

Using data from the CSPPT, a high-risk population for low folate, high tHcy, and stroke, the present study sought to address 2 related questions:

1. What is the prospective association between baseline PLT and tHcy levels and first stroke risk in Chinese hypertensive adults? We hypothesized that low PLT and elevated tHcy can jointly increase the risk of first stroke; and
2. Provided our hypothesis is correct, can folic acid treatment reduce the risk of first stroke associated with low PLT and high tHcy levels? We hypothesized that this subgroup would particularly benefit from folic acid treatment.

METHODS

STUDY DESIGN AND SETTING. All participants were part of the CSPPT (NCT00794885). Our paper adheres to the American Heart Association Journal's implementation of the Transparency and Openness Promotion Guidelines. The CSPPT was approved by the ethics committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number FWA00001263). All participants provided written informed consent.

The methods and primary results of the CSPPT have been previously reported (19). Briefly, the CSPPT was a multicommunity, randomized, double-blind, controlled trial conducted from May 2008 to August 2013 in 32 communities in China. Eligible participants were men and women age 45 to 75 years who had hypertension, defined as seated resting systolic blood pressure ≥ 140 mm Hg or diastolic blood

ABBREVIATIONS AND ACRONYMS

MPV = mean platelet volume

MTHFR =
methylentetrahydrofolate
reductase

PLT = platelet count

tHcy = total homocysteine

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