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COMMENT

Elevated albumin-to-creatinine ratio as a risk factor for stroke and homocysteine as an effect modifier in hypertensive Asian individuals

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The global lifetime risk of stroke in 2016 was estimated to be approximately 25% [1]. The risk was higher in Southeast Asia, East Asia, and Oceania than in other regions [1]. Albuminuria has emerged as an important risk factor for cardiovascular diseases, including stroke. A previous meta-analysis indicated that, independent of the estimated glomerular filtration rate (eGFR), a 25-mg/mmol increase in the albumin-to-creatinine ratio (ACR) was associated with a 10% increased risk of stroke [2]. However, information on the association of ACR with the risk of stroke in Asia and effect modifiers in this association has been limited.

He et al. investigated the ACR and the risk of first stroke in hypertensive Chinese patients treated with angiotensin-converting enzyme inhibitors (ACEIs) using China Stroke Primary Prevention Trial (CSPPT) data [3]. The CSPPT was a multicommunity, randomized, double-blind clinical trial that evaluated the effectiveness of enalapril plus folic acid therapy compared with enalapril alone for reducing the risk of first stroke. Figure 1 is the summary of their findings [3]. Patients with ACR ≥ 10 mg/g had a 1.5 times higher risk of stroke than those with ACR < 10 mg/g [3]. A high ACR was apparently more strongly associated with ischemic stroke than with hemorrhagic stroke [3]. In the CSPPT, the eligible participants were hypertensive patients aged 45–75 years without a history of physician-diagnosed stroke, myocardial infarction, heart failure, coronary revascularization, or congenital heart disease [4]. The average eGFR was over 70 mL/min/1.73 m^2 in all groups categorized according to ACR category. Therefore, their findings can be generalizable to hypertensive populations with fewer complications and can be broadly applicable in primary care [3]. Notably, in their study, hypertensive patients had been treated with ACEIs during the follow-up period [3]. Renin-angiotensin inhibitors decrease albuminuria [5–7]. Albuminuria at baseline or increased albuminuria following antihypertensive treatment initiation is a risk factor for end-stage renal disease, cardiovascular risk, and all-cause mortality [5–8]. The present findings suggest that ACR levels could be a risk factor for stroke even in Asians treated with renin-angiotensin inhibitors [3].

Their study also suggested that elevated total plasma homocysteine ([t]Hcy) would be an effect modifier in the association between high ACR and increased stroke risk. A recent study demonstrated a significant interaction between hypertension and tHcy levels and the risk of all-cause and cardiovascular disease mortality [9]. Hcy is a sulfur-containing amino acid formed as a byproduct of methyl-transfer reactions in methionine metabolism. As mentioned in their discussion [3], increased tHcy can promote atherosclerosis by inhibiting endothelial cell growth, promoting thrombosis, and increasing oxidative stress. A previous study using a mediation analysis suggested that tHcy can accelerate atherosclerosis partly via renal impairment [10], which may support the present findings from the CSPPT data. In the report by He et al., the stroke risk in the ACR ≥ 10 mg/g with tHcy ≥10 μmol/L group was 1.74 times higher than that in the highest ACR < 10 mg/g with tHcy<10 μmol/L group [3]. However, this significant association was diminished after adjustments for various baseline characteristics, including albumin, carotid intima-media thickness, and eGFR (Table S3 in their report) [3]. Further studies, such as those utilizing mediation analysis, may be needed to clarify the detailed pathway of the deleterious effect of high ACR combined with high tHcy.

Folic acid and vitamins play important roles in tHcy levels. A meta-analysis suggested that Hcy-lowering interventions in the form of vitamin B_6, B_9, or B_{12} supplementation alone or in combination, compared with a placebo, lowered the risk of stroke [11]. The primary analysis of the CSPPT data

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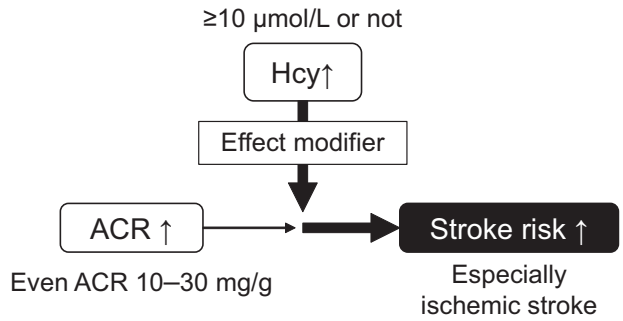

Fig. 1 The role of homocysteine (Hcy) in the association between the albumin-to-creatinine ratio (ACR) and stroke risk

demonstrated that the combined use of enalapril and folic acid, compared with enalapril alone, significantly reduced the risk of first stroke [4]. Therefore, it was expected that folic supplementation can also weaken the association between ACR and first stroke risk. The slight reduction in the hazard ratio of stroke for ACR ≥ 10 mg/g in the folic supplementation group compared with that in the nonsupplementation group [3] may imply that folic supplementation can attenuate the adverse effect of high ACR enhanced by hyperhomocysteinemia. However, no significant interaction between folic supplementation and ACR on the risk of first stroke was observed [3]. This implies that other treatments or actions should be considered to weaken the positive association between ACR and the risk of stroke. We should also consider the possibility that other factors elevating tHcy, such as nutrients, can be true effect modifiers.

The significant interaction between tHcy and ACR also implies that elevated ACR can be an effect modifier in the association between tHcy and stroke risk. Studies assessing the effects of tHcy should consider ACR levels. Furthermore, it is also suggested that preventing ACR elevation can reduce the adverse effects of tHcy. The impact of chronic kidney disease on lifetime stroke risk was found to be similar to that of hypertension in Asian populations [12]. Albuminuria should be assessed regularly from the viewpoint of stroke prevention, even in Asians without any overt kidney diseases.

Compliance with ethical standard

Conflict of interest The author declares no competing interests.

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