Homocysteine and the Risk of Stroke and Thromboembolism in Atrial Fibrillation: An Uncertain Role

To the Editor:
We read with great interest the article by Ay et al\(^1\) on the role of homocysteine in stroke and thromboembolic complications in patients with atrial fibrillation. Certainly, homocysteine has previously been shown to be associated with an increased risk of stroke,\(^2,3\) thrombosis,\(^4\) and impaired fibrinolysis;\(^5\) it is therefore important that its association with atrial fibrillation and the risk of left atrial thrombus and subsequent strokes be clarified.

Nonetheless, we have issues with certain aspects of the study by Ay et al.\(^1\) First, the numbers in groups studied are small (22 and 20, respectively). We agree that recruiting patients with an acute stroke and nonvalvular atrial fibrillation may not be easy, but in order to draw meaningful conclusions, we need to have larger numbers to avoid type II errors. A power calculation may be needed to convince the skeptics. Indeed, to show a (marginal) difference in mean/median homocysteine levels in stroke or ischemic heart disease between patients and controls, very large numbers (ranging from 110 to \(\sim 400\)) were previously required in each group.\(^6,7\)

Furthermore, a majority of the patients in the study by Ay et al\(^1\) had some form of vascular disease. Hypertension, which in itself is a risk factor for high homocysteine levels,\(^8,9\) was present in \(\sim 70\%\) in each group. Similarly, diabetes and ischemic heart disease were also present in many patients. Although there was no statistical difference between the groups, the patient numbers studied are probably not large enough to account for the many confounders and associated comorbidity that would influence homocysteine levels—indeed, statistical adjustments cannot fully account for all biological interactions and physiological processes.

Similarly, other important factors influencing the formation of left atrial thrombus—such as duration of atrial fibrillation, mean left atrial size for the 2 groups, and the use of antithrombotic agents or anticoagulants prior to the stroke—were not specified. Also, as the authors have rightly pointed out, homocysteine levels do rise in an acute stroke, and this may have some bearing on the levels measured.

Finally, is the association biologically plausible? We know that high homocysteine levels are associated with an increased risk of thrombosis in vascular disease, and atrial fibrillation is commonly associated with vascular disease. While the evidence is clear that atrial fibrillation confers a prothrombotic or hypercoagulable state,\(^10\) the possibility that increased homocysteine levels predict left atrial thrombosis in atrial fibrillation per se, independent of associated vascular disease and other “thrombogenic” factors, seems extremely remote. Indeed, as the authors have pointed out, Friedman\(^11\) did not show any difference in homocysteine levels between patients with atrial fibrillation and those in sinus rhythm. In this study, the patients who had a previous stroke did have a higher level of homocysteine than those who did not, but they were significantly older, and the authors did show a strong correlation between age and homocysteine levels. This study therefore refutes rather than corroborates the findings of Ay et al.\(^1\)

Thus, we respectfully disagree with the authors’ conclusion that their data are suggestive that hyperhomocysteinemia may be accepted as a risk factor for stroke and thromboembolism in patients with nonvalvular atrial fibrillation.

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Hyperhomocysteinemia and Left Atrial Thrombus in a Stroke Patient With Sinus Rhythm

To the Editor:
We read with great interest the recent article by Ay et al\(^1\) concerning the relationship between high plasma homocysteine levels and risk for left atrial thrombus formation in patients with stroke caused by nonvalvular atrial fibrillation. Their finding supports the thrombogenic role of high homocysteine in conditions associated with blood stasis. We recently observed a cardioembolic ischemic stroke from a left atrial thrombus formation in a man with sinus rhythm and a previous history of coronary heart disease. Laboratory analysis revealed an hyperhomocysteinemia.

A 56-year-old man was admitted to our department presenting with an acute visual disturbance and a mild speech disorder. He was a previous smoker with a 5-year history of hypertension, currently treated with an ACE inhibitor. At age 51 he had had an anteroapical myocardial infarction. Since that time he was under
treatment with aspirin. Neurologic examination revealed right upper quadrantanopsia and anomia aphasia. A CT brain scan showed a hypodense, ischemic lesion in the left temporoparietal region. Brain MRI confirmed the temporo-occipital ischemic lesion and disclosed an additional small ischemic lesion in the subcortical right hemisphere. EKG confirmed the signs of a previous anteroseptal myocardial infarction. Duplex ultrasonography of carotid and vertebral arteries did not show stenosis although it revealed an increased carotid artery intima-media thickness. MRI angiography was normal. Transhastoracic echocardiography revealed a mild left ventricular dysfunction (systolic ejection fraction of 50%) with apical akinesia and lateral wall and septal akinesia. Transesophageal echocardiography showed a slight left atrium enlargement and disclosed the presence of left atrial appendage thrombus, and spontaneous echo contrast. Laboratory analyses were performed and included blood chemistry, blood cell counts, erythrocyte sedimentation rate, and coagulation panel. He was started on anticoagulant treatment. Coagulopathy workup showed high fasting plasma homocysteine concentrations (23 μmol/L) and homozgyzosity for the 677C→T substitution polymorphism in the methylene tetrahydrofolate reductase-encoding gene.

Left atrial thrombus is infrequently detected in the presence of sinus rhythm, although it has been described in selected patients and, in these cases, is usually associated with additional cardiac pathologies. Patients in whom left atrial thrombus is detected in sinus rhythm are characterized by specific cardiac abnormalities (significant left ventricular dysfunction, valve disease, or previous episodes of AF). Significant left ventricular systolic and/or diastolic dysfunction predispose to LA thrombus formation via their secondary effect on LA hemodynamics. However, in the case reported here we observed a mild ventricular dysfunction. Transesophageal echocardiography also showed left atrial spontaneous echocardiographic contrast. This finding is unusual in patients with sinus rhythm. The presence of spontaneous echo contrast and the increased left atrial diameter are also strong markers of left atrial stasis. Transient paroxysms of AF may result in atrial dysfunction during the arrhythmia and after conversion to sinus rhythm, thus predisposing to LA thrombus formation. However, in the case reported here previous episodes of AF were not documented, although they cannot be excluded.

Interestingly, a recent study provided evidence of a strong association between homocysteine levels and risk of ischemic stroke in patients with preexisting coronary heart disease (defined as history of myocardial infarction ≥6 months but ≤5 years before enrollment in the study), or history of angina pectoris confirmed by appropriate investigations. The authors concluded that serum total homocysteine concentration is a strong predictor for incident ischemic stroke among patients at increased risk because of chronic coronary heart disease. The graded association observed was independent of traditional risk factors or inflammatory markers and indicated the importance of serum homocysteine levels in patients with preexisting cardiovascular disease.

Homocysteine is postulated to cause ischemic stroke via various mechanisms. It may promote atherogenesis by damaging the vascular matrix, increasing oxidative injury to arterial endothelium, and enhancing proliferation of vascular smooth muscle. High levels of homocysteine have been associated with extracranial carotid disease. It may also be prothrombotic and impair vasomotor regulation. Homocysteine is thus a biologically plausible factor in the pathogenesis of ischemic stroke.

Few studies have evaluated the relationship between homocysteine and stroke subtype. Hyperhomocysteinemia was associated in particular with stroke due to large-artery disease and small-artery disease. These studies support the hypothesis that homocysteine is a causal risk factor for atherosclerotic cerebrovascular disease. On the other hand, the recent studies of Ay et al and Tanne et al outline the strong association also between hyperhomocysteinemia and cardioembolic stroke. Accordingly, the cardioembolic stroke reported here occurred in a patient with hyperhomocysteinemia and preexisting coronary heart disease. Prospective studies are needed to evaluate the possible benefit from interventions that lower total homocysteine concentrations in selected high-risk patients.

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Response

We thank Drs Cupini and De Simone and Drs Nadar and Lip for their interest in our article. In the referred study, we demonstrated that mean serum homocysteine level was higher in patients with left atrial (LA) thrombus as compared with patients without LA thrombus in a cohort of consecutive patients with stroke due to nonvalvular atrial fibrillation (AF). The difference was highly significant (P<0.001).

Drs Nadar and Lip argue that our study might be subject to type II error owing to insufficient power. A type II error occurs when the null hypothesis is not rejected in situations where the alternative hypothesis is true. It is indeed correct that the risk of such an error is greater for small studies. However, in the present situation, we are able to reject the null hypothesis, so by definition, we cannot commit a type II error. It is also true that small studies have less power, which makes it more difficult to reject the null hypothesis. Nonetheless, this does not in any way invalidate the conclusion when an effect is large enough that one is able to reject the null hypothesis, despite a small sample size. Increasing sample size in the present situation would likely result in more significant probability values.

In the case of positive studies, like ours, one would be more concerned about having a type I error, the probability of the observed effect occurring due to chance. We report a P value of 0.001, which makes the probability of having a false-positive result less than 1 in 1000. This is apparently much better than the customarily accepted 0.05 limit in clinical scientific studies.

Drs Nadar and Lip are correct that the majority of our patients had some form of vascular disease; the study was conducted in...
patients with stroke. Stroke patients with nonvalvular AF are usually older and more commonly harbor vascular risk factors such as hypertension.\textsuperscript{3,4} Unequal distribution of risk factors across study groups, however, can confound univariate associations. Logistic regression is a valid method to adjust for such confounders. In the present case, a multivariate logistic regression analysis revealed that high serum homocysteine was independently associated with the presence of LA thrombus ($P=0.017$). This analysis included major factors known to be associated with both LA thrombus formation and high serum homocysteine. However, we recognize that there is always a risk in clinical studies that poorly recognized or yet unknown variables can confound their results.

Unlike our study, the article cited\textsuperscript{5} by Drs Nadar and Lip reporting a relationship between high serum homocysteine and prior history of stroke in patients with AF did not adjust for confounders. It is not possible to conclude that the observed effect was age-dependent without performing a logistic regression analysis. Only after such an analysis can one presume that this study may refute our findings.

We would like to point out that the relationship between high serum homocysteine and LA thrombus identified in our study does not directly translate into the stroke risk in patients with AF. A separate study that also includes nonstroke patients is needed in order to conclude that, as Drs Nadar and Lip exercise in their title, high serum homocysteine is a risk factor for stroke and thromboembolism in AF. We believe our findings will trigger such studies. We concur with Drs Cupini and De Simone that future research should also focus on the role of high serum homocysteine in conditions associated with cardiac stasis other than AF.

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