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ORIGINAL RESEARCH

Plasma Total Homocysteine Level Is Related to Unfavorable Outcomes in Ischemic Stroke With Atrial Fibrillation

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BACKGROUND: Unlike patients with stroke caused by other mechanisms, the effect of elevated plasma total homocysteine (tHcy) on the prognosis of patients with both ischemic stroke and atrial fibrillation (AF) is unknown. This study aimed to evaluate the association between tHcy level and the functional outcome of patients with AF-related stroke.

METHODS AND RESULTS: We included consecutive patients with AF-related stroke between 2013 and 2015 from the registry of a real-world prospective cohort from 11 large centers in South Korea. A 3-month modified Rankin Scale score ≥3 was considered an unfavorable outcome. Since tHcy is strongly affected by renal function, we performed a subgroup analysis according to the presence of renal dysfunction. A total of 910 patients with AF-related stroke were evaluated (mean age, 73 years; male sex, 56.0%). The mean tHcy level was 11.98±8.81 μmol/L. In multivariable analysis, the tHcy level (adjusted odds ratio, 1.04; 95% CI, 1.01–1.07, per 1 μmol/L) remained significantly associated with unfavorable outcomes. In the subgroup analysis based on renal function, tHcy values above the cutoff point (≥14.60 μmol/L) showed a close association with the unfavorable outcome only in the normal renal function group (adjusted odds ratio, 3.10; 95% CI, 1.60–6.01). In patients with renal dysfunction, tHcy was not significantly associated with the prognosis of AF-related stroke.

CONCLUSIONS: A higher plasma tHcy level was associated with unfavorable outcomes in patients with AF-related stroke. This positive association may vary according to renal function but needs to be verified in further studies.

Key Words: atrial fibrillation ■ homocysteine ■ ischemic stroke ■ prognosis ■ vitamin

Homocysteine is a sulfur-containing amino acid and is a by-product of methionine metabolism.[1] Studies have shown that an elevated plasma total homocysteine (tHcy) level is closely associated with the occurrence, progression, and recurrence of ischemic stroke.[2–6] Therefore, a high tHcy level is considered an independent risk factor for ischemic stroke. In addition, tHcy has been noted to be a modifiable risk factor for ischemic stroke because its level decreases up to 25% with vitamin B supplements.[7] However, vitamin therapy gradually lost researchers' interest, as it failed to prove a distinct preventive effect in the initial analyses of several clinical trials (eg, VISP [Vitamin Intervention for Stroke Prevention] trial, VITATOPS [Vitamins to Prevent Stroke] trial).[8,9]

Ischemic stroke is a heterogeneous disease that occurs because of various pathological mechanisms.[10]

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CLINICAL PERSPECTIVE

What Is New?

- Even in cardioembolic stroke associated with atrial fibrillation, total homocysteine was associated with the prognosis of stroke.
- Renal function appears to have a significant effect on this association.

What Are the Clinical Implications?

- Recently, vitamin therapy for patients with stroke has been shown to have a benefit in the limited patient group.
- If we use total homocysteine to classify patients with atrial fibrillation–related stroke into high-risk groups, it may be helpful in selecting subjects for which this vitamin therapy is effective.

Nonstandard Abbreviations and Acronyms

K-ATTENTION	Korean Atrial Fibrillation Evaluation Registry in Ischemic Stroke Patients
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
tHcy	total homocysteine
VISP	Vitamin Intervention for Stroke Prevention
VITATOPS	Vitamins to Prevent Stroke

Therefore, the preventive effect of vitamin therapy against ischemic stroke may get masked because of the heterogeneity of patient characteristics. This is a plausible hypothesis as shown by the subgroup analysis of VISP and VITATOPS trials, which included only small-vessel diseases that showed significant benefits from vitamin therapy.[8,9,11] Meanwhile, several studies have analyzed the various influences of tHcy according to stroke mechanisms.[12,13] Overall, tHcy showed a close association with ischemic stroke caused by large-vessel disease or small-vessel disease.[1,2,12,13] Conversely, there seemed to be no clear association between tHcy and cardioembolic stroke.

However, an elevated tHcy level also seems to be involved in the structural or electrophysiological remodeling of the heart.[14–17] It is associated with left atrial enlargement, myocyte size increase, cardiac fibrosis, and remodeling of the sodium/potassium ion channel, leading to the development of a cardiac environment prone to atrial fibrillation (AF).[14–17] Given this theoretical background, the tHcy level seems to be able to have a significant effect on the occurrence of ischemic stroke in patients with AF.[16,18] However, there is a lack of research on the effect of tHcy on the prognosis of patients who have ischemic stroke and AF at the same time (collectively termed *AF-related stroke*). Therefore, we aimed to evaluate whether high plasma tHcy levels in patients with AF-related stroke are associated with unfavorable functional outcomes. Recent meta-analyses of previous clinical trials related to vitamin therapy showed that the interpretation of the results may differ depending on the renal function.[11,19] Therefore, we also decided to perform subgroup analyses according to renal function.

METHODS

Study Population

Our study is a substudy of the K-ATTENTION (Korean Atrial Fibrillation Evaluation Registry in Ischemic Stroke Patients) study, a real-world cohort comprising prospective stroke registries of 11 large centers in South Korea, with data collected between January 2013 and December 2015.[20] AF was documented using electrocardiography, 24-hour Holter monitoring, or continuous electrocardiogram monitoring during hospitalization. For all patients with AF-related stroke, broad etiological evaluations, including brain magnetic resonance imaging, echocardiography, and laboratory examinations were performed according to each center's protocol. From this large registry, we included consecutive patients with AF-related stroke who did not receive thrombolytic therapy. We then sequentially excluded participants on the basis of the following exclusion criteria: (1) no available tHcy or 3-month modified Rankin Scale (mRS) data; (2) presence of valvular AF; (3) age <18 years; and (4) visit >7 days from the onset of symptoms. Thus, a total of 941 participants remained. However, during our data analysis, we found that only 31 participants had congestive heart failure (CHF). Considering the statistical bias that this low prevalence may have, 910 participants were included in the final analyses.

This retrospective study was approved by the Institutional Review Board (IRB) at Samsung Medical Center (No. SMC-2016-07-011). The Institutional Review Board waived the requirement to obtain written informed consent from the study participants because of the retrospective design using only anonymous information. All experiments were performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations. All data and materials related to this article are included in the main text and supplemental material.

Risk Factor Assessments

We assessed the demographic, clinical, and vascular risk factors, including age, sex, body mass index, hypertension, diabetes, dyslipidemia, types of AF, ischemic heart disease, CHF, history of stroke, initial National Institutes of Health Stroke Scale (NIHSS) score, systolic and diastolic blood pressure, $CHADS_2$ score, and discharge medications.[21] AF was classified as paroxysmal or sustained AF.[21] The initial NIHSS score was rated on a daily basis from admission to discharge by well-trained neurologists who were not involved in this study. The $CHADS_2$ score was calculated on the basis of the established scoring formula consisting of items from CHF, hypertension, age ≥75 years, diabetes (each 1 point), and history of stroke or transient ischemic attack (2 points).[22] We also reviewed discharge medications, including antiplatelet agents, oral anticoagulants, and statins. Among oral anticoagulants, non–vitamin K antagonist oral anticoagulants, and vitamin K antagonists were separately evaluated.

Laboratory examination results were obtained within the first 24 hours of admission, including glucose profiles (glycosylated hemoglobin: %, fasting blood sugar, mg/dL), cholesterol profiles (mg/dL), inflammatory markers (eg, white blood cell counts: $\times 10^3/\mu L$, hs-CRP [high-sensitivity C-reactive protein]: mg/dL), D-dimer (μg/mL), estimated glomerular filtration rate (eGFR), and tHcy (μmol/L).[21] eGFR was calculated from the Modification of Diet in Renal Disease formula as follows: $eGFR=175\times serum\ creatinine^{-1.154}\times age^{-0.203}\times 0.742$ (for females). We defined *renal dysfunction* as eGFR <60 mL/min per 1.73 m^2.[23] Urine test results were not included in this study, and therefore urinary albumin excretion values were not included in the analysis.

Outcome Factor Assessment

As a primary outcome, we rated the 3-month modified Rankin Scale (mRS) scores. Based on this rating, we dichotomized participants into favorable (mRS 0–2) and unfavorable (mRS 3–6) groups.[20] We also assessed early neurological deterioration events, which were defined as an increase ≥2 in the total NIHSS score or ≥1 in the motor NIHSS score within the first 72 hours of admission.[21]

Statistical Analysis

All statistical analyses were performed using SPSS version 20.0 (IBM, SPSS, Chicago, IL, USA). Univariate analyses for the evaluation of possible predictors of unfavorable outcomes were performed using Student's *t*-test or the Mann-Whitney *U*-test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Based on the results of the univariate analyses, variables with $P<0.10$ and eGFR were introduced into the multivariable logistic regression analysis (model 1). Moreover, for sensitivity analysis, we compared the analysis results by adjusting the $CHADS_2$ score as a confounder instead of multiple overlapping variables (eg, age, CHF, diastolic blood pressure, and fasting glucose) (model 2).

The plasma tHcy level is strongly affected by renal function, and vitamin B therapy in patients with eGFR <60 mL/min per 1.73 m^2 has been reported to be toxic.[3,5] Therefore, we performed a subgroup analysis on the effects of tHcy on unfavorable outcomes according to the presence or absence of renal dysfunction. To clearly show the difference between these two groups, we plotted the relationship between the tHcy level and the unfavorable outcome for each group using the restricted cubic spline function. Furthermore, to understand the underlying pathological mechanisms between tHcy and the prognosis of AF-related stroke, the association between tHcy and various risk factors was evaluated using simple linear regression analysis. All variables with $P<0.05$ were considered significant in this study.

RESULTS

A total of 910 patients with AF-related stroke were analyzed (mean age, 73 years; male sex, 56.0%; mean initial NIHSS score, 6). The mean tHcy level was 11.98±8.81 μmol/L, and 350 (38.5%) participants had an unfavorable outcome (mRS 3–6). Other baseline characteristics are presented in Table 1. In this study, the tHcy level was correlated with male sex, hypertension, $CHADS_2$ score, high-density lipoprotein cholesterol levels, D-dimer, eGFR, and unfavorable outcomes (Table S1).

In the univariate analysis, unfavorable outcomes were significantly associated with age, male sex, body mass index, dyslipidemia, initial NIHSS score, early neurological deterioration, diastolic blood pressure, $CHADS_2$ score, use of discharge oral anticoagulants and statins, and levels of fasting glucose, total cholesterol, triglycerides, white blood cells, hs-CRP, and D-dimer (Table 2). In the multivariable logistic regression analysis, the tHcy level remained significant after adjusting for confounders (adjusted odds ratio [aOR], 1.04; 95% CI, 1.01–1.07, per 1 μmol/L). Age (aOR, 1.04; 95% CI, 1.01–1.06, per 1 year), initial NIHSS score (aOR, 1.26; 95% CI, 1.20–1.31), and white blood cell counts (aOR, 1.08; 95% CI, 1.01–1.16, per $1\times 10^3/\mu L$) were also associated with unfavorable outcomes. On the other hand, discharge oral anticoagulants (for non–vitamin K antagonist oral anticoagulants: aOR, 0.31; 95% CI, 0.15–0.63; for vitamin K antagonists: aOR, 0.39; 95% CI, 0.24–0.64) and discharge statin use (aOR, 0.45; 95% CI, 0.27–0.75) were associated with favorable outcomes. Even when adjusted using $CHADS_2$ score

Table 1. Baseline Characteristics of the Study Population (n=910)

Demographic and clinical factors	
Age, y (IQR)	74 (67–80)
Sex, male, n (%)	510 (56.0)
Visit time, d (SD)	1±1
Body mass index, kg/m^2 (IQR)	23.1 (21.2–25.2)
Hypertension, n (%)	633 (69.6)
Diabetes, n (%)	269 (29.6)
Dyslipidemia, n (%)	278 (30.5)
Type of atrial fibrillation, n (%)	
Paroxysmal	506 (55.6)
Sustained	404 (44.4)
Ischemic heart disease, n (%)	118 (13.0)
History of stroke, n (%)	305 (33.5)
Initial NIHSS score (IQR)	3 (1–10)
Systolic BP, mm Hg (IQR)	140 (127–161)
Diastolic BP, mm Hg (IQR)	85 (76–97)
$CHADS_2$ score (IQR)	3 (3–4)
Discharge anti-PLT, n (%)	243 (26.7)
Discharge OAC, n (%)	
No	231 (25.4)
NOAC	122 (13.4)
VKA	557 (61.2)
Discharge statin, n (%)	663 (77.3)
Laboratory factors	
HbA_{1c}, % (IQR)	5.8 (5.5–6.4)
Fasting blood sugar, mg/dL (IQR)	109 (94–133)
Total cholesterol, mg/dL (IQR)	160 (137–187)
LDL cholesterol, mg/dL (IQR)	96 (73–121)
HDL cholesterol, mg/dL (IQR)	46 (37–55)
Triglyceride, mg/dL (IQR)	85 (63–115)
White blood cell, ×10^3/μL (IQR)	7.70 (6.25–9.53)
High-sensitivity CRP, mg/dL (IQR)	0.39 (0.13–1.63)
D-dimer, μg/mL (IQR)	0.67 (0.33–1.53)
eGFR, mL/min per1.73 m^2 (IQR)	75.36 (58.73–95.20)
Total homocysteine, μmol/L (IQR)	10.30 (7.90–13.90)
Outcome factors	
Early neurological deterioration, n (%)	89 (12.1)
3-mo outcome, n (%)	
Favorable outcome (mRS 0–2)	560 (61.5)
Unfavorable outcome (mRS 3–6)	350 (38.5)

anti-PLT indicates antiplatelet agent; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, non–vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; and VKA, vitamin K antagonist.

on behalf of several variables, tHcy still showed a close association with unfavorable outcomes (aOR, 1.04; 95% CI, 1.01–1.07), and with other variables showing

Table 2. Baseline Characteristics of Patients With Favorable and Unfavorable Outcomes Based on a 3-Month Modified Rankin Scale

	Favorable (mRS 0–2) (n=560)	Unfavorable (mRS 3–6) (n=350)	*P* value
Age, y (IQR)	72 (66–78)	78 (72–83)	<0.001
Sex, male, n (%)	345 (61.6)	165 (47.1)	<0.001
Visit time, d (IQR)	0 (0–1)	0 (0–1)	0.713
Body mass index, kg/m^2 (IQR)	23.5 (21.6–25.6)	22.6 (20.4–24.8)	<0.001
Hypertension, n (%)	385 (68.8)	248 (70.9)	0.502
Diabetes, n (%)	168 (30.0)	101 (28.9)	0.713
Dyslipidemia, n (%)	188 (33.6)	90 (25.7)	0.012
Type of atrial fibrillation, n (%)			0.364
Paroxysmal	318 (56.8)	188 (53.7)	
Sustained	242 (43.2)	162 (46.3)	
Ischemic heart disease, n (%)	71 (12.7)	47 (13.4)	0.743
History of stroke, n (%)	178 (31.8)	127 (36.3)	0.162
Initial NIHSS score (IQR)	2 (1–4)	11 (5–18)	<0.001
Systolic BP, mm Hg (IQR)	140 (126–160)	142 (130–165)	0.304
Diastolic BP, mm Hg (IQR)	87 (77–97)	82 (73–95)	0.064
$CHADS_2$ score (IQR)	3 (3–4)	4 (3–4)	<0.001
Discharge anti-PLT, n (%)	158 (28.2)	85 (24.3)	0.193
Discharge OAC, n (%)			<0.001
No	83 (14.8)	148 (42.3)	
NOAC	89 (15.9)	33 (9.4)	
VKA	388 (69.3)	169 (48.3)	
Discharge statin, n (%)	449 (83.8)	214 (66.5)	<0.001
HbA_{1c}, % (IQR)	5.8 (5.5–6.4)	5.8 (5.4–6.3)	0.271
Fasting glucose, mg/dL (IQR)	105 (92–126)	119 (100–146)	<0.001
Total cholesterol, mg/dL (SD)	158 (135–184)	164 (141–192)	0.022
LDL cholesterol, mg/dL (IQR)	95 (72–119)	101 (73–125)	0.119
HDL cholesterol, mg/dL (IQR)	45 (37–55)	47 (38–56)	0.157
Triglyceride, mg/dL (IQR)	90 (66–121)	80 (60–105)	<0.001
White blood cell, ×10^3/μL (IQR)	7.40 (6.06–8.96)	8.20 (6.71–10.82)	<0.001
High-sensitivity CRP, mg/dL (IQR)	0.29 (0.09–1.11)	0.71 (0.21–2.70)	<0.001
D-dimer, μg/mL (IQR)	0.50 (0.28–0.98)	1.15 (0.59–2.40)	<0.001
eGFR, mL/min per 1.73 m^2 (IQR)	76.36 (60.32–95.22)	73.54 (55.92–95.02)	0.354
Total homocysteine, μmol/L (IQR)	10.20 (7.90–13.15)	10.88 (7.90–15.28)	0.080

(*Continued*)

Table 2. Continued

	Favorable (mRS 0–2) (n=560)	Unfavorable (mRS 3–6) (n=350)	*P* value
Early neurological deterioration, n (%)	15 (3.3)	74 (26.1)	<0.001

anti-PLT indicates antiplatelet agent; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; and VKA, vitamin K antagonist.

similar results (Table 3). In our data, the cutoff point for the unfavorable outcome of tHcy calculated on the basis of the receiver operating characteristic curve was 14.60 μmol/L. When analyzed on the basis of this point, patients with tHcy above the cutoff point were associated with an unfavorable outcome 1.80 times more than those with tHcy lower than that (Table S2).

In our data, patients with renal dysfunction had significantly higher tHcy values than patients with normal renal function (14.06±7.06 μmol/L versus 11.21±9.26 μmol/L; *P*<0.001). Nevertheless, in the subgroup analysis by renal function, tHcy levels above cutoff value (tHcy ≥14.60 μmol/L) showed a close association with unfavorable outcomes only in the normal renal function group (aOR, 3.10; 95% CI, 1.60–6.01). In the presence of renal dysfunction, the tHcy level was not significantly associated with the prognosis of AF-related stroke (Table 4 and Figure).

DISCUSSION

In this study, we found that high plasma tHcy levels were associated with unfavorable outcomes in patients with AF-related stroke. This relationship showed different patterns according to the presence of renal dysfunction. In patients with AF-related stroke, the renal function not only affected the plasma tHcy levels, but also seemed to influence the relationship between tHcy and stroke outcomes.

The exact mechanisms explaining the close relationship between tHcy and unfavorable outcomes are unclear. However, we suggest several possible hypotheses. First, an elevated tHcy level may promote intracardiac thrombus formation, leading to stroke recurrence. As mentioned earlier, tHcy causes structural deformation of the heart, which increases blood stasis and leads to the development of thrombi.[14,15,17] tHcy can also activate the prothrombotic tendency of blood, which promotes the development of an intracardiac thrombus.[7,17,24] This generated thrombus can result in additional embolic events, leading to unfavorable outcomes. In support of this statement, the tHcy level showed close associations with D-dimer levels and $CHADS_2$ scores and had a marginal statistical tendency with early neurological deterioration events (Table S1). Second, elevated tHcy levels can create a vulnerable brain environment, which can hinder functional recovery after stroke. In previous studies, elevated tHcy levels had a close association with endothelial dysfunction through oxidative stress or subclinical inflammation.[1,3,7] If the endothelium is impaired, the blood-brain barrier breaks down and the cerebral vessels lose their autoregulatory vasodilator function, which can lead to a more severe initial stroke and disruption of recovery.[1,25,26] In addition, tHcy has also been confirmed to have negative effects on viability, proliferation, and differentiation of the neural stem cells by promoting autophagy, and this mechanism may lead to a reduced poststroke neural repair ability.[27] Finally, mechanisms other than AF, such as atherosclerosis, may have been involved. It is known that one-sixth of patients with AF experience strokes attributable to mechanisms unrelated to AF.[16,28] tHcy was also found to have a close association with the development of atherosclerosis and the plaque instability in previous studies.[2,29,30] Given that tHcy was also related to several vascular risk factors and ischemic heart disease, which is an atherosclerotic disease, in our data, it is possible that tHcy affected the unfavorable outcome via a mechanism other than AF.

Interestingly, in our study, tHcy functioned as a prognostic marker only in patients with normal renal function. The exact mechanisms of this phenomenon are unclear. However, we speculate the following hypotheses:

1. In patients with renal dysfunction, tHcy levels are so high that they have already exceeded pathological levels.[31] Therefore, a slight tHcy change in these patients may be difficult to induce large clinical differences.
2. Old age and several potent vascular risk factors are frequently found in patients with renal dysfunction. Therefore, the influence of tHcy may be relatively obscured by these factors and may appear weak.

Indeed, in our data, tHcy showed a statistically significant biological interaction with renal dysfunction (*P*=0.034). However, our findings require careful interpretation, and verification through analysis of other study populations should also be made.

There are several caveats to our study findings. First, this is essentially a retrospective study. Thus, although tHcy was closely related to the unfavorable outcome of patients with AF-related stroke, this implies only an association and not a causal relationship. Additional prospective studies are needed to confirm this causal

Table 3. Multivariable Logistic Regression Analysis of Possible Predictors for Unfavorable Outcomes (mRS 3–6)

	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Model 1*				
Age	1.07 (1.05–1.08)	<0.001	1.04 (1.01–1.06)	0.003
Male sex	0.56 (0.42–0.73)	<0.001	0.77 (0.50–1.19)	0.242
Body mass index	0.90 (0.86–0.94)	<0.001	0.98 (0.92–1.04)	0.510
Dyslipidemia	0.69 (0.51–0.92)	0.013	0.63 (0.39–1.03)	0.065
Initial NIHSS score	1.29 (1.24–1.33)	<0.001	1.26 (1.20–1.31)	<0.001
Diastolic BP	0.99 (0.98–1.00)	0.142	0.99 (0.98–1.01)	0.315
Discharge OAC		<0.001		<0.001
No	Ref	Ref	Ref	Ref
NOAC	0.21 (0.13–0.34)	<0.001	0.31 (0.15–0.63)	0.001
VKA	0.24 (0.18–0.34)	<0.001	0.39 (0.24–0.64)	<0.001
Discharge statin	0.38 (0.28–0.53)	<0.001	0.45 (0.27–0.75)	0.002
Fasting glucose	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.01)	0.230
Total cholesterol	1.00 (1.00–1.01)	0.020	1.00 (1.00–1.01)	0.214
White blood cell	1.15 (1.10–1.21)	<0.001	1.08 (1.01–1.16)	0.026
D-dimer	1.43 (1.29–1.58)	<0.001	1.10 (0.99–1.21)	0.066
eGFR	1.00 (1.00–1.00)	0.514	1.00 (1.00–1.00)	0.633
Total homocysteine	1.03 (1.01–1.05)	0.009	1.04 (1.01–1.07)	0.007
Model 2†				
$CHADS_2$ score	1.42 (1.21–1.65)	<0.001	1.30 (1.04–1.63)	0.023
Male sex	0.56 (0.42–0.73)	<0.001	0.74 (0.49–1.11)	0.146
Body mass index	0.90 (0.86–0.94)	<0.001	0.96 (0.90–1.02)	0.175
Dyslipidemia	0.69 (0.51–0.92)	0.013	0.68 (0.43–1.08)	0.103
Initial NIHSS score	1.29 (1.24–1.33)	<0.001	1.25 (1.21–1.31)	<0.001
Discharge OAC		<0.001		<0.001
No	Ref	Ref	Ref	Ref
NOAC	0.21 (0.13–0.34)	<0.001	0.32 (0.16–0.64)	0.001
VKA	0.24 (0.18–0.34)	<0.001	0.36 (0.22–0.57)	<0.001
Discharge statin	0.38 (0.28–0.53)	<0.001	0.50 (0.31–0.81)	0.005
Total cholesterol	1.00 (1.00–1.01)	0.020	1.00 (1.00–1.01)	0.112
White blood cell	1.15 (1.10–1.21)	<0.001	1.07 (1.00–1.14)	0.043
D-dimer	1.43 (1.29–1.58)	<0.001	1.13 (1.03–1.25)	0.012
eGFR	1.00 (1.00–1.00)	0.514	1.00 (1.00–1.00)	0.638
Total homocysteine	1.03 (1.01–1.05)	0.009	1.04 (1.01–1.07)	0.007

BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, non–vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; and VKA, vitamin K antagonist.

*Adjusted with $P<0.10$ in univariate analysis and eGFR.

†$CHADS_2$ score was used instead of age, congestive heart failure, diastolic BP, and fasting glucose.

relationship. Second, we only analyzed the tHcy levels at admission. Analysis of outpatient clinic data may provide more information on the effect of changes in tHcy levels for up to 3 months on the prognosis and clarify the causal relationship. Third, tHcy showed a skewed distribution in our study population, which means that the association between tHcy and unfavorable outcome may not show the same 4% effect in all ranges of tHcy values. The high frequency of some patients with high tHcy values above the threshold may have led to an association between the two. Fourth, the variables related to the patient's risk factors were defined on the basis of the medical history at the time of admission. Therefore, some of these may have been an underestimation of what they really are. The most representative example is CHF, where there were only 31 (3.3%) cases in our data. This is a significantly lower number than previous studies performed on patients with AF-related stroke, and the authors judged that this was a very low prevalence at a level that could have a

Table 4. Multivariable Logistic Regression Analysis of Possible Predictors for Unfavorable Outcomes (mRS 3–6) in Patients With and Without Renal Dysfunction*

	Normal renal function (n=664)		Renal dysfunction (n=246)	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.05 (1.02–1.08)	<0.001	0.98 (0.93–1.04)	0.547
Male sex	0.68 (0.41–1.13)	0.138	0.94 (0.37–2.41)	0.899
Body mass index	1.00 (0.92–1.08)	0.920	0.96 (0.85–1.09)	0.551
Dyslipidemia	0.68 (0.37–1.23)	0.201	0.43 (0.16–1.13)	0.086
Initial NIHSS score	1.25 (1.18–1.31)	<0.001	1.32 (1.19–1.46)	<0.001
Diastolic BP	0.99 (0.97–1.00)	0.075	1.02 (0.99–1.05)	0.235
Discharge OAC		0.003		0.053
No	Ref	Ref	Ref	Ref
NOAC	0.30 (0.13–0.68)	0.004	0.31 (0.07–1.47)	0.140
VKA	0.40 (0.22–0.72)	0.002	0.27 (0.09–0.79)	0.017
Discharge statin	0.40 (0.22–0.73)	0.003	0.61 (0.22–1.72)	0.351
Fasting glucose	1.00 (1.00–1.01)	0.486	1.01 (1.00–1.01)	0.206
Total cholesterol	1.00 (1.00–1.01)	0.284	1.00 (0.99–1.02)	0.524
White blood cell	1.12 (1.03–1.22)	0.006	1.04 (0.92–1.18)	0.515
D-dimer	1.03 (0.88–1.21)	0.737	1.22 (0.98–1.53)	0.078
tHcy ≥14.60 μmol/L	3.10 (1.60–6.01)	0.001	0.94 (0.39–2.30)	0.899

BP indicates blood pressure; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, non–vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; tHcy, total homocysteine; and VKA, vitamin K antagonist.

*Renal dysfunction was defined as eGFR <60 mL/min per 1.73 m^2.

statistically large bias and excluded it from the analysis. Therefore, it is necessary to consider these points when interpreting our findings. Finally, information on vitamin therapy or other laboratory markers associated with tHcy (eg, folate, vitamins B_6 and B_{12}) would have been more helpful in interpreting the results.

We demonstrated that high plasma tHcy levels were associated with unfavorable outcomes in patients with AF-related stroke using data from 11 large centers in South Korea. Recently, several studies have interpreted that the reason vitamin therapy is ineffective in stroke prevention is that the by-product of cyanocobalamin

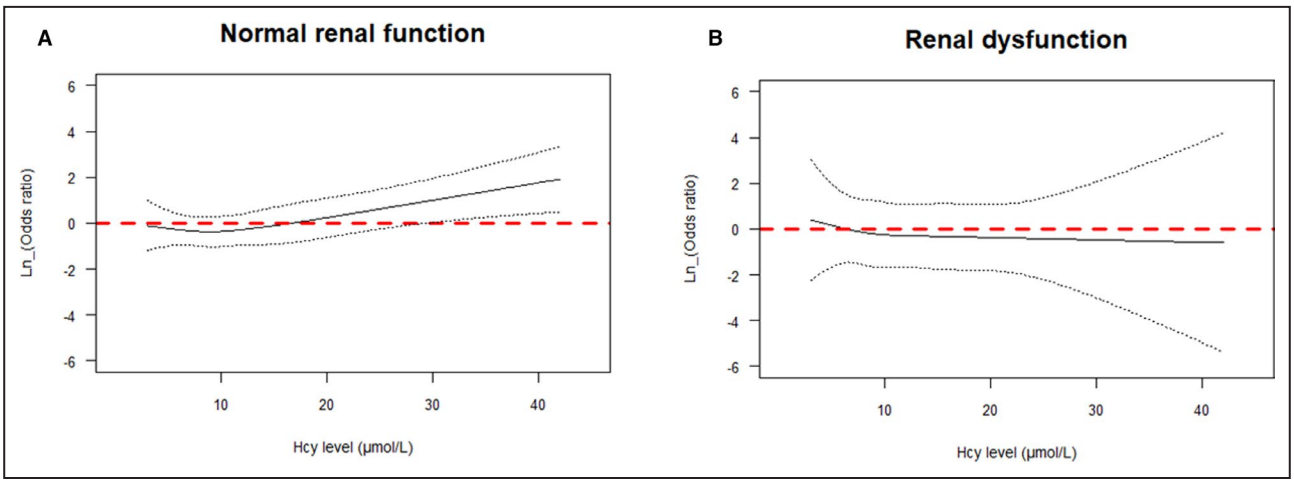

Figure. Association between plasma total homocysteine levels and unfavorable outcomes in patients with AF-related stroke.

In patients with normal renal function, plasma total homocysteine levels showed a clear positive correlation with unfavorable outcomes (**A**). However, this positive correlation between these two was not evident in patients with renal dysfunction (**B**). Hcy indicates homocysteine.

accumulates.[19,32,33] In addition, post hoc analysis or meta-analysis of the VISP and VITATOPS trials revealed that this phenomenon is more pronounced in patients with renal dysfunction, whose metabolite clearance is not good.[19,33,34] Due to this, the effect of vitamin therapy on stroke prevention is reevaluated, and interest in tHcy research is also increasing. At this point, our findings will help classify appropriate high-risk groups for vitamin therapy. However, further prospective studies are needed to validate our findings.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Simple linear regression analysis between total homocysteine and demographic, clinical, and laboratory risk factors

	β (95% CI)	*P* value
Age	0.055 (-0.003 to 0.113)	0.064
Male sex	2.197 (1.051 to 3.344)	< 0.001
Body mass index	0.019 (-0.157 to 0.194)	0.833
Hypertension	1.662 (0.420 to 2.904)	0.009
Diabetes	-0.036 (-1.292 to 1.221)	0.956
Dyslipidemia	0.530 (-0.714 to 1.775)	0.403
Sustained atrial fibrillation	0.077 (-1.077 to 1.232)	0.895
Ischemic heart disease	1.652 (-0.052 to 3.356)	0.057
History of stroke	0.661 (-0.553 to 1.876)	0.285
Initial NIHSS score	0.026 (-0.055 to 0.106)	0.532
$CHADS_2$ score	1.012 (0.371 to 1.653)	0.002
HbA1c	-0.143 (-0.506 to 0.220)	0.440
Fasting glucose	-0.010 (-0.024 to 0.004)	0.163
Total cholesterol	-0.004 (-0.019 to 0.011)	0.611
LDL cholesterol	-0.015 (-0.031 to 0.002)	0.077
HDL cholesterol	0.031 (0.002 to 0.059)	0.035
Triglyceride	0.005 (-0.005 to 0.015)	0.313
White blood cell	0.081 (-0.105 to 0.266)	0.393
High-sensitivity CRP	0.020 (-0.021 to 0.061)	0.336
D-dimer	0.254 (0.014 to 0.495)	0.038
eGFR	-0.023 (-0.035 to -0.011)	< 0.001
Early neurological deterioration	1.885 (-0.173 to 3.943)	0.073
Unfavorable outcome (mRS 3-6)	1.649 (0.475 to 2.823)	0.006

NIHSS = National Institutes of Health Stroke Scale, LDL = low-density lipoprotein, HDL = high-density lipoprotein, CRP = C-reactive protein, eGFR= estimated glomerular filtration rate, mRS = modified Rankin Scale

Table S2. Multivariable logistic regression analysis of possible predictors for unfavorable outcomes using cut-off point of total homocysteine

	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age	1.07 [1.05-1.08]	< 0.001	1.04 [1.01-1.06]	0.003
Male sex	0.56 [0.42-0.73]	< 0.001	0.80 [0.52-1.24]	0.320
Body mass index	0.90 [0.86-0.94]	< 0.001	0.98 [0.92-1.04]	0.523
Dyslipidemia	0.69 [0.51-0.92]	0.013	0.64 [0.39-1.04]	0.070
Initial NIHSS score	1.29 [1.24-1.33]	< 0.001	1.25 [1.20-1.31]	< 0.001
Diastolic BP	0.99 [0.98-1.00]	0.142	0.99 [0.98-1.01]	0.281
Discharge OAC		< 0.001		< 0.001
No	Ref	Ref	Ref	Ref
NOAC	0.21 [0.13-0.34]	< 0.001	0.32 [0.16-0.65]	0.002
VKA	0.24 [0.18-0.34]	< 0.001	0.40 [0.24-0.65]	< 0.001
Discharge statin	0.38 [0.28-0.53]	< 0.001	0.46 [0.28-0.76]	0.002
Fasting glucose	1.01 [1.00-1.01]	< 0.001	1.00 [1.00-1.01]	0.260
Total cholesterol	1.00 [1.00-1.01]	0.020	1.00 [1.00-1.01]	0.178
White blood cell	1.15 [1.10-1.21]	< 0.001	1.08 [1.01-1.16]	0.026
D-dimer	1.43 [1.29-1.58]	< 0.001	1.09 [0.99-1.21]	0.093
eGFR	1.00 [1.00-1.00]	0.514	1.00 [1.00-1.00]	0.591
tHcy ≥ 14.60 μmol/L	2.06 [1.50-2.85]	< 0.001	1.80 [1.08-2.98]	0.023

NIHSS = National Institutes of Health Stroke Scale, BP = blood pressure, OAC = oral anticoagulant, NOAC = non-vitamin K antagonist oral anticoagulants, VKA = vitamin K antagonist, eGFR = estimated glomerular filtration rate, tHcy = total homocysteine