High Levels of Apolipoprotein B/AI Ratio Are Associated With Intracranial Atherosclerotic Stenosis

Jong-Ho Park, MD, PhD; Keun-Sik Hong, MD, PhD; Eun-Ja Lee, MD, PhD; Juneyoung Lee, PhD; Dong-Eog Kim, MD, PhD

Background and Purpose—The apolipoprotein B (apoB)/apoAI ratio is recognized as a better indicator of cardiovascular disease than other cholesterol measures. Whether intracranial or extracranial atherosclerosis is more closely associated with an increased apoB/apoAI ratio has not been investigated.

Methods—A total of 464 statin or fibrate naïve Korean patients with acute ischemic stroke was categorized into 3 groups: intracranial (ICAS, n=236), extracranial (n=44), and no cerebral atherosclerotic stenosis (n=184). The apoB/apoAI ratio and demographics, including the presence of metabolic syndrome, were compared among the groups.

Results—The ICAS group showed a higher apoB/apoAI ratio (0.81±0.02) than both the extracranial atherosclerotic stenosis (0.74±0.03) and no cerebral atherosclerotic stenosis (0.72±0.02) groups (P=0.002). The ratio was substantially increased (0.93±0.03) in patients with advanced ICAS (≥3 intracranial stenoses). With a multivariable analysis, the highest apoB/apoAI ratio quartile was an independent predictor of ICAS (OR, 2.13; 95% CI, 1.05 to 4.33). A dose–response relationship was observed between the presence of advanced ICAS and the apoB/apoAI ratio quartiles (OR, 4.03; 95% CI, 1.26 to 12.88 for the second quartile; OR, 4.88; 95% CI, 1.54 to 15.49 for the third quartile; and OR, 7.79; 95% CI, 2.41 to 25.16 for the fourth quartile when referenced to the first quartile). Patients having more metabolic syndrome components were more likely to have ICAS, advanced ICAS, and a higher apoB/apoAI ratio (P<0.001 for all).

Conclusions—A higher apoB/apoAI ratio is a predictor of ICAS rather than of extracranial atherosclerotic stenosis or no cerebral atherosclerotic stenosis. The apoB/apoAI ratio might be a biomarker for ICAS in Asian patients with stroke. (Stroke. 2011;42:3040-3046.)

Key Words: apolipoprotein AI ■ apolipoprotein B ■ atherosclerosis ■ intracranial

A polipoprotein B (apoB) levels better reflect the total number of potentially atherogenic particles than the low-density lipoprotein cholesterol (LDL-C) level does. The oxidation of apoB creates multiple proinflammatory products and propagates atherogenesis within the arterial wall. In contrast, apolipoprotein A-I (apoAI), which is the major apolipoprotein in high-density lipoprotein cholesterol (HDL-C), initiates reverse cholesterol transport from blood vessels to the liver. ApoAI also has antioxidant and anti-inflammatory effects. Accordingly, the apoB/apoAI ratio has been recognized as a better predictor of cardiovascular risk than any other cholesterol measure.

Metabolic syndrome (MetS) is associated with diverse lipid disturbances, including reduced HDL-C levels, raised fasting and postprandial triglyceride-rich lipoproteins (mainly very-low-density lipoprotein), and increased small, dense LDL particles. The apoB/apoAI ratio has been reported to be higher in patients with MetS than in those without MetS. In a recent study of patients with ischemic stroke, MetS was independently associated with intracranial atherosclerotic stenosis (ICAS) compared with extracranial atherosclerotic stenosis (ECAS) and no cerebral atherosclerotic stenosis (NCAS).

MetS and ICAS are likely to have common underlying mechanisms for the raised atherogeneity and reduced antioxidative activity. Taking these into account, an increased apoB/apoAI ratio might be more closely related to ICAS than to ECAS or NCAS in patients with stroke.

This study was performed to compare the serum levels of the apoB/apoAI ratio and MetS among patients with ischemic stroke with ICAS, ECAS, and NCAS and to investigate whether ICAS has a higher apoB/apoAI ratio than ECAS and NCAS.

Methods

Patients

We prospectively recruited consecutive patients with acute ischemic stroke (≤7 days of onset) with relevant neuroimaging findings from
March 2008 through September 2010. Patients excluded were the following: those who had been on statin or fibrate before admission because these drugs affect serum apolipoprotein levels,4 those who underwent incomplete vascular imaging and laboratory tests, those who had strokes of other determined etiologies or transient ischemic attacks with negative diffusion-weighted images, and those who did not provide informed consent. We collected data on demographics, risk factors, blood pressure, fasting glucose levels, total cholesterol levels, LDL-C levels, HDL-C levels, triglyceride levels, apoB levels, apoAI levels, and abdominal circumference. To investigate the cardioembolic source, electrocardiography and echocardiography were performed in all patients, and transequiocardioangiography and 24-hour Holter monitoring were performed for selected patients at the discretion of the responsible physician. In all patients aged <50 years, the prothrombotic tendency for stroke was evaluated.

All patients underwent neuroimaging and vascular imaging. Brain MRI and MR angiography were performed in most patients, and CT and CT angiography were performed in MR-contraindicated or noncompliant patients. Additional conventional angiography was performed in 44 patients. The 3-dimensional time-of-flight technique was used for evaluating intracranial vessels, and 3-dimensional contrast-enhanced MR angiography was used for extracranial vessels. Two independent reviewers (J.-H.P. and E.-J.L.), who were blinded to the clinical information, evaluated the vascular images. The x statistics for the concordance rate showed a high degree of agreement (x=0.86, P<0.01). Discrepancies were resolved by consensus.

Informed consent was obtained from all subjects, and the study protocol was approved by the Institutional Review Board of Kwan-dong University Myongji Hospital.

Classification of Cerebral Atherosclerosis
Irrespective of index stroke mechanisms, patients were classified into 3 groups based on their vascular imaging and other clinical data as follows: (1) the ICAS group had a significant stenosis (symptomatic or asymptomatic) in the proximal portion of the middle, anterior, or posterior cerebral artery; the basilar artery; or the intracranial portion of the internal carotid artery or vertebral artery (V3); (2) the ECAS group had a significant stenosis in the extracranial portion of the internal carotid artery or vertebral artery (V1 to V3); and (3) the patients with NCAS had no or <50% stenosis in the intracranial or extracranial arteries. The arteries with acute cardioembolic occlusion or with decreased vessel signals due to proximal steno-occlusive lesions were not regarded as having a true stenosis.

Twenty-eight patients who had both ICAS and ECAS were categorized into the ICAS group. Significant stenosis was defined as ≥50% stenosis in the intracranial or extracranial arteries.13,14 We also quantified intra- and extracranial stenosis based on the number of stenotic arteries. We presupposed that patients having ≥3 stenoses were determined to have “advanced” lesions.

Definition of MetS and Blood Tests
The definition of MetS, which was determined by the American Heart Association/National Heart, Lung, and Blood Institute,13 was modified with the Asia-Pacific waist circumference criteria provided by the World Health Organization Western Pacific Region (2000).16 MetS was diagnosed if patients had ≥3 of the following: (1) increased waist circumference (≥90 cm in men or ≥80 cm in women); (2) high blood pressure (systolic blood pressure ≥130 mm Hg and/or a diastolic blood pressure ≥85 mm Hg measured at least 10 days after stroke onset); (3) high fasting glucose (≥100 mg/dL); (4) high triglyceride levels (≥150 mg/dL); and (5) low HDL-C levels (<40 mg/dL for men, <50 mg/dL for women). Trained nurses measured the waist circumference using a measuring tape positioned at the highest point of the iliac crest.

Blood samples for fasting concentrations were drawn in the morning after an overnight fast for >8 hours. Serum levels of total cholesterol, triglyceride, HDL-C, and LDL-C were assayed by enzymatic techniques (Wako Pure Chemical Industries, Ltd, Osaka, Japan). The apoB and apoAI levels were measured by immunope-
were included in this study. The remaining 295 patients were excluded due to the following reasons: 198 had prior statin or fibrate use, 21 had transient ischemic attacks without relevant neuroimaging findings, 12 had strokes of other determined etiology, 12 had missing data for MetS, 10 had missing apolipoprotein tests, 4 had no vascular imaging, 4 had no informed consent, and 34 had other reasons for exclusion. Trial of Org 10172 in Acute Stroke Treatment classification of the index strokes were 177 (38.1%) large artery atherosclerosis (137 intracranial versus 40 extracranial atherosclerosis), 150 (32.3%) small vessel occlusions, 99 (21.3%) cardioembolisms, and 38 (8.2%) strokes of undetermined etiology. Among 464 patients, 236 (50.9%) were classified as ICAS (28 [6.0%] patients had both ICAS and ECAS), 44 (9.5%) as ECAS, and 184 (39.7%) as NCAS. Advanced atherosclerotic stenosis (≥3) was found in 83 (35.2%) patients with ICAS and 8 (11.1%) patients with ECAS.

Baseline characteristics for each of the ICAS, ECAS, and NCAS groups are given in Table 1. Compared with the ECAS and/or NCAS groups, the ICAS group showed significantly higher levels of systolic blood pressure, glucose, LDL-C, and triglyceride levels as well as higher frequencies of hypertension, diabetes mellitus, coronary artery disease, and MetS, whereas HDL-C levels, male, and smoking frequencies were lower.

**ApoB/ApoAI Ratio, MetS, and ICAS**

Although no differences in apoB levels were found, apoAI levels differed across the groups. ApoAI levels were lowest in the ICAS group, intermediate in the ECAS group, and highest in the NCAS group (Table 1). This caused the apoB/apoAI ratios (mean±SE) to be significantly different between the groups: 0.81±0.02 in the ICAS group, 0.74±0.03 in the ECAS group, and 0.72±0.02 in the NCAS group (P=0.002). Although the 95% CIs of the ICAS and ECAS groups marginally overlapped due to a wide 95% CI in the ECAS group, there was a significant difference between the ICAS and the NCAS groups (P=0.001; Table 1 and Figure 1A).

The values of the apoB/apoAI ratios of the ICAS group remained stable after excluding 28 patients who had both ICAS and ECAS from the ICAS group (0.81±0.02). In addition, patients with advanced ICAS had a higher apoB/apoAI ratio compared with those with 1 or 2 lesions of ICAS and with no ICAS (P<0.001; Figure 1B).

Patients were stratified into quartiles according to the distribution of their serum apoB/apoAI ratios for males and females. The resulting range of sex-specific quartiles were <0.60 (first quartile), 0.60 to 0.73 (second quartile), 0.74 to 0.91 (third quartile), and >0.91 (fourth quartile) for males and <0.62 (first quartile), 0.62 to 0.73 (second quartile), 0.74 to 0.87 (third quartile), and >0.87 (fourth quartile) for females. Figure 2 demonstrates the relationship of the apoB/apoAI ratio quartiles to the presence of ICAS or ECAS, the number of ICAS lesions (0 to ≥3), the presence of MetS, and the number of MetS components. Patients with higher quartiles of the apoB/apoAI ratio had a higher incidence of ICAS (P<0.001; Figure 2A) and had greater numbers of ICAS (P<0.001; Figure 2B). However, these associations were not observed in those with ECAS. MetS was more frequent in patients with higher apoB/apoAI ratio quartiles (P<0.001; Figure 2C). Patients with higher quartiles of the apoB/apoAI ratio were more likely to have a greater number of MetS components (P<0.001; Figure 2D). Patients with a greater number of MetS components were more likely to have ICAS (P<0.001; Figure 3A) and a greater number of ICAS lesions (P<0.001; Figure 3B). Patients with more MetS components had a higher apoB/apoAI ratio: 0.64±0.02 for 0 to 2 MetS components; 0.79±0.02 for 3 MetS components; and 0.89±0.02 for ≥3 MetS components (P<0.001; Figure 4). No association, however, was noted between the MetS components and the number of ECAS.

**Association of ApoB/ApoAI Ratio With ICAS**

For entry into the multivariable models, we selected the covariates that were significant (P<0.05) for ICAS in uni-
variate analyses (Table 1). These included age, sex, smoking, hypertension, diabetes, coronary artery disease, MetS, and LDL-C. The results of the univariate and multiple logistic regression analyses for predictors of ICAS and advanced ICAS are given in Table 2. In these analyses, ICAS was compared with non-ICAS (ECAS and NCAS), whereas advanced ICAS was compared with non-ICAS and nonadvanced (1 or 2) ICAS.

For ICAS, the univariate analyses showed that patients with higher apoB/apoA1 ratio quartiles compared with those with the lowest quartile were associated with an increased risk for ICAS. Other significant variables associated with increasing ICAS risk were age, hypertension, diabetes, coronary artery disease, MetS, and the third and fourth quartiles of LDL-C levels, whereas smoking was less likely to be associated with ICAS than with ECAS or NCAS. Multivariable analyses showed that the highest apoB/apoA1 ratio quartile was significantly associated with ICAS (OR, 2.13; 95% CI, 1.05 to 4.33). Other independent variables for ICAS were hypertension (1.75; 1.04 to 2.93), diabetes (2.09; 1.31 to 3.32), coronary artery disease (2.68; 1.09 to 6.57), and MetS (1.81; 1.06 to 3.08), but LDL-C quartiles had no significant association with ICAS.

For advanced ICAS, univariate analyses demonstrated that patients with higher apoB/apoA1 ratio quartiles were associated with an increased risk for advanced ICAS. Age, female sex, hypertension, diabetes, MetS, and the highest LDL-C quartile were associated with advanced ICAS, whereas smoking was negatively associated with it. Multivariable analyses indicated that advanced ICAS had a dose–response relationship with apoB/apoA1 ratio quartiles: the second quartile, OR, 4.03 (95% CI, 1.26 to 12.88); the third quartile, 4.88 (1.54 to 15.49); and the fourth quartile, 7.79 (2.41 to 25.16), when referenced to the first quartile. Other independent predictors were age (OR, 1.03; 95% CI, 1.00 to 1.06), diabetes (2.07; 1.18 to 3.65), and MetS (3.66; 1.36 to 9.83). The LDL-C quartiles did not show any significant association with advanced ICAS.

The highest quartile of the apoB/apoA1 ratio, diabetes, and MetS were independent predictors for both the presence of ICAS and advanced ICAS. The magnitude of the association was greater with advanced ICAS than with the presence of
ICAS. The apoB/apoAI ratio as a continuous variable was also independently associated with advanced ICAS (OR, 7.87; 95% CI, 2.47 to 25.10; see Supplemental Table I for full data; http://stroke.ahajournals.org).

After adjusting for 5 MetS components instead of the presence of MetS, the dose–response relationship between the apoB/apoAI ratio and advanced ICAS remained robust; the adjusted ORs for advanced ICAS was 3.96 for the second quartile (95% CI, 1.23 to 12.75), 4.94 for the third quartile (95% CI, 1.54 to 15.88), and 7.75 for the fourth quartile (95% CI, 2.31 to 26.05). Among the MetS components, only high fasting glucose was an independent predictor of advanced ICAS (OR, 3.19; 95% CI, 1.71 to 5.94, see Supplemental Table II for full data).

**Discussion**

This study suggests that an increased apoB/apoAI ratio might be a risk factor for ICAS. Several studies have indicated an association of the apoB/apoAI ratio and the risk of stroke and extracranial carotid stenosis, but no prior study has demonstrated an association between the apoB/apoAI ratio and ICAS. Patients with ICAS had a greater apoB/apoAI ratio than those with NCAS, and they showed a tendency for a higher apoB/apoAI ratio when compared with those with ECAS. Particularly, the ratio was markedly increased in advanced ICAS. As a result, patients with the highest quartile of the apoB/apoAI ratio had a 2-fold increased risk of ICAS. The risk of advanced ICAS increased monotonically with a higher apoB/apoAI ratio, and it was increased approximately...
Our study clearly demonstrates the triangular associations among the apoB/apoAI ratio, MetS, and ICAS. As the apoB/apoAI ratio increased, the severity of ICAS and MetS components increased as well as the presence of ICAS and MetS. The findings of the current study conform to prior studies. In patients with MetS, apoB-containing small, dense LDL increases and apoAI-containing HDL decreases. The close association between a higher apoB/apoAI ratio and MetS has been demonstrated in multiple studies.8–10 In a Korean study of patients with ischemic stroke, MetS was most frequently observed in patients with ICAS, and it was an independent risk factor for ICAS.11

The finding of no association between ECAS and the apoB/apoAI ratio in this study contrasts with findings of other studies in which an increased apoB/apoAI ratio was associated with a progression in the intima-media thickness and in higher intima-media thickness values of extracranial carotid arteries.10,20,21 This discrepancy might be attributed to ethnic differences, and, so, our findings need to be replicated in subsequent studies. One study demonstrated an ethnic difference in the association of MetS between ICAS and ECAS. In nonwhite populations, MetS was more closely associated with ICAS than with ECAS, whereas in whites, MetS was associated with ECAS but not with ICAS.27

In a previous study, intracranial arteries had a greater activity of antioxidant enzymes than extracranial arteries.28 In our population, patients with ICAS had a lower value of apoAI, a marker of antioxidant properties, compared with those with ECAS and NCAS. However, the apoB level, a marker of atherogenic properties, did not differ. Therefore, a more selective loss of antioxidant activities in ICAS might explain our findings of a lower apoB/apoAI ratio in ICAS compared with ECAS and NCAS. This study has several limitations. First, we compared the apoB/apoAI ratios within ischemic stroke populations. Because a comparison between patients with ICAS and a healthy population was not performed, the increased apoB/apoAI ratio as a risk for ICAS should be interpreted with caution. Second, our data were obtained in a single center, and, accordingly, an extrapolation of our findings to the general Korean stroke population or other ethnic populations might be limited. Third, apoB and apoAI were measured in an acute period of ischemic stroke and at variable time intervals from stroke onset to blood sampling within 7 days from stroke onset, which potentially jeopardizes the validity of our findings. However, apoB and apoAI levels have been reported to be generally stable during the 4 weeks after a stroke,29 and the time intervals from onset to admission in this

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<tr>
<th>Table 2. Crude and Adjusted ORs for Predictors of ICAS and Advanced ICAS Using Univariate and Multiple Logistic Regression Analyses, Respectively</th>
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<tr>
<td><strong>ICAS</strong></td>
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<tr>
<td><strong>Crude OR (95% CI)</strong></td>
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<td><strong>P</strong></td>
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<tr>
<td>Age, 1-y difference</td>
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<tr>
<td>Male</td>
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<td>Smoking</td>
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<td>Hypertension</td>
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<td>Diabetes mellitus</td>
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<td>CAD</td>
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<td>MetS</td>
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**ApoB/apoAI quartiles‡**

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<th>First</th>
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<tr>
<td>Second</td>
<td>1.49 (0.90–2.49)</td>
<td>0.124</td>
<td>1.34 (0.75–2.39)</td>
<td>0.325</td>
</tr>
<tr>
<td>Third</td>
<td>1.80 (1.06–3.05)</td>
<td>0.030</td>
<td>1.40 (0.75–2.62)</td>
<td>0.289</td>
</tr>
<tr>
<td>Fourth</td>
<td>2.02 (1.19–3.41)</td>
<td>0.009</td>
<td>1.31 (0.68–2.51)</td>
<td>0.417</td>
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| Second | 1.92 (1.14–3.24) | 0.015 | 1.66 (0.91–3.01) | 0.098 | 5.09 (1.67–15.55) | 0.004 | 4.03 (1.26–12.88) | 0.019 |
| Third | 1.79 (1.06–3.02) | 0.029 | 1.25 (0.66–2.36) | 0.487 | 7.45 (2.50–22.16) | <0.001 | 4.88 (1.54–15.49) | 0.007 |
| Fourth | 3.30 (1.92–5.67) | <0.001 | 2.13 (1.05–4.33) | 0.037 | 13.26 (4.54–38.79) | <0.001 | 7.79 (2.41–25.16) | 0.001 |

**ICAS indicates intracranial atherosclerotic stenosis; CAD, coronary artery disease; MetS, metabolic syndrome; LDL-C, low-density lipoprotein cholesterol; apo, apolipoprotein; ECAS, extracranial atherosclerotic stenosis; NCAS, no atherosclerotic stenosis; OR, odds ratio; CI, confidence interval.**

†Compared with ECAS and NCAS as a reference group.

‡Ranges for sex-specific quartiles were <0.60, 0.60–0.73, 0.74–0.91, and >0.91 for males; <0.62, 0.62–0.73, 0.74–0.87, and >0.87 for females.
study did not differ among the ICAS, ECAS, and NCAS groups. Therefore, the time point of measuring apoB and apoAI is less likely to affect our findings.

ICAS might be the most common and important atherosclerotic subtype in the cerebrovascular bed worldwide as well as in Asian populations. However, studies on the risk factors of ICAS have been limited, and biological markers, which can be therapeutic targets, in ICAS have not been well defined like in ECAS. The current study suggests that the apoB/apoAI ratio is a promising biomarker for ICAS and sets forth the rationale for larger studies of diverse populations.

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Disclosure

None.

References

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