Increased Risk for Intracranial Arterial Stenosis in Subjects With Coronary Artery Calcification

Hyung-Geun Oh, MD, PhD; Pil-Wook Chung, MD, PhD; Eun-Jung Rhee, MD, PhD

Background and Purpose—Intracranial arterial stenosis (ICAS) is considered an important cause of stroke in Asians. Coronary artery calcification (CAC) is a surrogate marker for subclinical atherosclerosis. We aimed to analyze the association of ICAS assessed by transcranial Doppler ultrasonography and CAC in middle-aged Korean population.

Methods—This study included 10,550 participants (81.3% men, mean age 43 years) from a health screening program, in whom transcranial Doppler ultrasonography was used to detect >50% intracranial stenosis based on criteria modified from the stroke outcomes and neuroimaging of intracranial atherosclerosis trial. Multidetector computed tomography was used to assess coronary artery calcium score (CACS). CAC grade (0, 1–100, and >100) was defined by CACS.

Results—The subjects with CAC showed significantly higher proportion of subjects with ICAS compared with those without CAC (4.4% versus 2.8%; P<0.01). Conversely, the subjects with ICAS showed significantly higher proportion of subjects with CAC (24.8% versus 17.1%; P<0.01). When logistic regression analysis was performed with ICAS as the dependent variable, the presence of CAC showed significantly increased risk for ICAS after adjustment for confounding variables (odds ratio, 1.439; 95% confidence interval, 1.095–1.891). When CACS grade was included in the model, the odds ratio for ICAS was the highest in subjects with CACS >400 compared with those with CACS=0 (odds ratio, 2.754; 95% confidence interval, 1.205–2.936).

Conclusions—The risk for ICAS was significantly increased in middle-aged Korean subjects with CAC compared with that in those without CAC. These findings suggest the possibility of a separate undetected atherosclerotic focus in subjects with 1 atherosclerotic event. (Stroke. 2015;46:151-156. DOI: 10.1161/STROKEAHA.114.006996.)

Key Words: coronary artery disease ■ intracranial atherosclerosis ■ transcranial Doppler ultrasound ■ vascular calcification

Cardiovascular disease is the leading cause of death worldwide.1 Atherosclerosis is a common mechanism leading to the development of cardiovascular diseases, and ischemic stroke and coronary artery disease share common risk factors, atherosclerotic processes, and pathophysiologic mechanisms.2 Coronary artery disease is considered the most important cause of mortality in stroke patients.3,4 However, coronary artery disease and stroke are somewhat different with respect to the contribution of individual atherosclerotic risk factors.

Intracranial arterial stenosis (ICAS) is the process of atherosclerosis that affects large intracranial arteries.5 ICAS is considered an especially important cause of stroke in Asians.6,7 The prevalence of asymptomatic ICAS in the Asian population is relatively high, and ICAS is a more common cause of ischemic stroke in Asians than in Caucasians, suggesting that ICAS is an important underlying cause of stroke in Asians.8-12 ICAS can be diagnosed using different imaging modalities. Among them, transcranial Doppler (TCD) ultrasonography is a safe, noninvasive, and inexpensive diagnostic method.13 Although the accuracy of TCD ultrasonography in measuring the degree of stenosis varies among reported studies, it is advantageous for detecting ICAS because it provides real-time flow information in contrast to static imaging methods, such as computed tomographic angiography or magnetic resonance angiography.14,15

Coronary artery calcification (CAC) is a surrogate marker for subclinical atherosclerosis and is known from previously reported studies to reflect atherosclerotic burden.16,17 Increased coronary artery calcification score (CACS) is known to correlate with the risk of cardiovascular disease and various metabolic diseases.18,19 A recent study reported the association of increased CACS with development of ischemic stroke in a large CAC-based cohort.20

There is no single imaging method for the determination of whole-body atherosclerotic status. Furthermore, there is no report on the association between ICAS and CAC in healthy subjects. We investigated the relationship between ICAS, diagnosed by TCD ultrasonography, and CAC, assessed by multidetector computed tomography, in relatively young healthy Korean adults.

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From the Department of Neurology, Soonchunhyang University College of Medicine, Cheonan, Korea (H.-G.O.); and Departments of Neurology (P.-W.C.) and Endocrinology and Metabolism (E.-J.R.), Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea.

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Correspondence to Eun-Jung Rhee, MD, PhD, Division of Endocrinology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 108 Pyung-dong, Jongro-ku, Seoul 110–746, Korea. E-mail hongsiri@hanmail.net

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Methods

Participants

This cross-sectional study was part of the Kangbuk Samsung Health Study, in which the subjects were the participants in a medical health checkup program at the Health Promotion Center of Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. The study was approved by the institutional review board of Kangbuk Samsung Hospital (KBC13051), which exempted the requirement of informed consent as we used only deidentified data routinely collected during the health screening process.

Measurement of CACS

Computed tomography scan was performed using a LightSpeed VCT XTe-64 slice multidetector computed tomography scanner (GE Healthcare, Tokyo, Japan) in both Seoul and Suwon centers using the same standard scanning protocol: 2/5-mm thickness, 400 ms rotation time, 120 kV tube voltage, and 124 mAs (310 mA, 0.4 s) tube current under retrosternal ECG-gated dose modulation. No informed consent was obtained from the subject because no contrast media was used. Radiation dose for noncontrast computed tomography is low, with typical effective dose of ≈1.0 mSv, about the same dose of radiation of 1.5 screening mammograms performed.

A total CACS was determined by the sum of the individual scores for the 4 major epicardial coronary arteries. Agatston CAC measurement and scoring were previously described. The presence of CAC was defined as CACS >0. Subjects were divided into 3 groups or 4 groups according to the CACS: CACS=0, 0<CACS≤100, and CACS>100 or CACS=0, 0<CACS≤100, 100<CACS≤400, and CACS>400.

TCD Ultrasonography Evaluation and Diagnosis of ICAS

TCD ultrasonography was performed by a trained ultrasonographer using a single-channel TCD ultrasonography (Nicolet SONARA TCD system, Natus Medical Incorporated, San Carlos, CA). The following mean flow velocity (MFV) cut-offs on TCD ultrasonography were used for identification of ≥50% stenosis according to the SONIA (stroke outcomes and neuroimaging of intracranial ath- erosclerosis) trial criteria: middle cerebral artery MFV >100 cm/s, distal internal carotid artery MFV >90 cm/s, vertebral artery MFV >80 cm/s, and basilar artery MFV >80 cm/s. Because the anterior cerebral artery and posterior cerebral artery were not evaluated in the SONIA trial, we adapted previously validated criteria for detection of ICAS in these vessels: anterior cerebral artery MFV ≥80 cm/s and posterior cerebral artery MFV ≥80 cm/s. ICAS was diagnosed if ≥1 of the studied arteries showed evidence of stenosis. Subjects with poor temporal windows were excluded from the study. Subjects were divided into 4 groups according to the number of stenotic intracranial arteries: 0, 1, 2, and ≥3.

Statistical Analyses is described in the online-only Data Supplement.

Results

General characteristics of the participants are presented in Table 1. Mean age of the participants was 43 years, and 81% of the participants were men. The mean body mass index was 24 kg/m², which indicated that the participants were slightly overweight (Table 1). Thirty participants (0.3%) had a history of ischemic stroke and 73 participants (0.7%) had a history of myocardial infarction.

Comparisons of the Parameters According to the Presence or Absence of CAC

Among the participants, 17.3% (n=1827) had CAC (Table 2). A higher proportion of subjects with CAC were men compared with those without CAC (87.2% versus 80.0%). Subjects with CAC were older than those without CAC (Table 2). Most of the metabolic parameters were worse in subjects with CAC compared with those without CAC. The proportion of subjects with a history of ischemic stroke or myocardial infarction was higher in subjects with CAC than in those without CAC (Table 1). The proportion of subjects in the CAC group with a history of smoking was higher than that in the group without CAC (59.2% versus 48.9%). When the proportion of subjects with ICAS was compared between groups, a significantly higher proportion of subjects with CAC had ICAS, determined by TCD ultrasonography, than those without CAC (Table 2). When the proportion of subjects with ICAS was compared among the groups divided by CACS, the proportion significantly increased from the first group (CACS=0) to fourth group (CACS>400; Figure 1).

Comparisons of the Parameters According to the Presence or Absence of ICAS

Among the participants, 3.1% (n=323) had ICAS determined by TCD ultrasonography (Table 3). The proportion of men was smaller and mean age was higher in subjects with ICAS than those without ICAS (65.9% versus 81.7% and 45.5±10.6 versus 43.2±8.8). Although the mean body mass index was

Table 1. General Characteristics of the Participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43.3±8.8</td>
</tr>
<tr>
<td>Sex: male, %</td>
<td>8572 (81.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.5±3.1</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>116±13</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>74.6±9.8</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dL</td>
<td>99.0±17.9</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>203.4±36.0</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>139.4±90.3</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>53.2±13.1</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>128.5±32.5</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.7±0.6</td>
</tr>
<tr>
<td>Ln (CACS+1)</td>
<td>0.57±1.4</td>
</tr>
<tr>
<td>Proportion of subjects with history of diabetes mellitus, %</td>
<td>479 (4.5)</td>
</tr>
<tr>
<td>Proportion of subjects with history of hypertension, %</td>
<td>1886 (17.9)</td>
</tr>
<tr>
<td>Proportion of subjects with history of ischemic stroke, %</td>
<td>30 (0.3)</td>
</tr>
<tr>
<td>Proportion of subjects with history of myocardial infarction, %</td>
<td>73 (0.7)</td>
</tr>
<tr>
<td>Proportion of subjects who has ever smoked, %*</td>
<td>5348 (50.7)</td>
</tr>
<tr>
<td>Proportion of subjects with in ICAS, %</td>
<td>323 (3.1)</td>
</tr>
<tr>
<td>Proportion of subjects with coronary artery calcification, %†</td>
<td>1827 (17.3)</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or number (%). CACS indicates coronary artery calcium score; HbA1c, glycatedhemoglobin; HDL-C indicates high-density lipoprotein cholesterol; ICAS, intracranial artery stenosis; LDL-C, low-density lipoprotein cholesterol; and ln(CACS+1), logarithmized form of coronary artery calcium score+1.

*Ever-smoker was defined as one who has ever smoked ≥5 packs of cigarettes during the life time.

†The presence of coronary artery calcification is defined by CACS>0.
lower in subjects with ICAS than in those without ICAS, other metabolic parameters were worse in the ICAS group (Table 3). When the proportion of subjects with CAC was compared between the groups divided by ICAS, the proportion of subjects with CAC was significantly higher in those with ICAS compared with those without ICAS (24.8 versus 17.1%; Table 3).

Among the subjects with ICAS, 2.5% (n=260) showed 1 stenotic artery, 0.5% (n=50) showed 2 stenotic arteries, and 0.1% (n=13) showed stenosis in >3 arteries. When individual arteries were counted, 2.6% (n=274) showed stenosis in middle cerebral artery, 0.3% in distal internal carotid artery (n=28), 0.1% (n=8) in vertebral artery, 0.4% (n=38) in basilar artery, and 0.5% (n=56) in anterior cerebral artery. No subject showed stenosis in posterior cerebral artery. As the number of stenotic intracranial arteries increased from 0 to ≥3, the proportion of subjects with CAC significantly increased (Figure 2).

Logistic Regression Analysis With ICAS as the Dependent Variable
When logistic regression analysis was performed with ICAS as the dependent variable, the subjects with CAC showed a significantly increased odds ratio (OR) for ICAS after adjustment for confounding variables (1.439; 95% confidence interval, 1.095–1.891; Model 1; Table 4). When the CACS grade was included in the model, the group with the highest CACS (CACS>100) showed a significantly increased OR of 2.754 (95% confidence interval, 1.334–5.685) for ICAS compared with the group with CACS=0 after adjustment for confounding variables (Model 3; Table 4).

Logistic Regression Analysis With Presence of CAC as Dependent Variable
When logistic regression analysis was performed with presence of CAC as the dependent variable, presence of ICAS did not show significantly increased risk of CAC after adjustment for confounding variables (Model 1; Table in the online-only Data Supplement). When the individual intracranial arteries were included in the model, the presence of stenosis in basilar artery showed the highest risk for the presence of CAC (OR, 3.586; 95% confidence interval, 1.439–9.83).

![Figure 1. Comparison of the proportion of subjects with intracranial arterial stenosis (ICAS) according to the groups divided by coronary artery calcium score (CACS).](http://stroke.ahajournals.org/DownloadedFrom)
In this study performed in a middle-aged population, 17.3% of the subjects showed CAC as defined by CACS>0 and only 3.1% had ICAS diagnosed by TCD ultrasonography. Subjects with CAC were older, and a significantly higher proportion of subjects with CAC had ICAS than those without CAC. The proportion of subjects with ICAS increased as the CACS increased from 0 to >400. Conversely, subjects with ICAS were older and a significantly higher proportion had CAC compared with those without ICAS. The proportion of subjects with CAC increased as the number of stenotic intracranial arteries increased from 0 to ≥3. When the OR for ICAS was analyzed with logistic regression analysis, CAC showed a significantly increased OR of 1.439 for ICAS after adjustment for confounding variables, which showed a significantly increased OR in the highest CACS (CACS>100). However, when logistic regression analysis was performed with presence of CAC as the dependent variable, the presence of ICAS did not show increased risk for CAC. The results of this study indicate the significance of the 2 assessment methods for atherosclerosis, ICAS and CAC in the prediction of atherosclerotic burden.

Discussion

In this study performed in a middle-aged population, 17.3% of the subjects showed CAC as defined by CACS>0 and only 3.1% had ICAS diagnosed by TCD ultrasonography. Subjects with CAC were older, and a significantly higher proportion of subjects with CAC had ICAS than those without CAC. The proportion of subjects with ICAS increased as the CACS increased from 0 to ≥400. Conversely, subjects with ICAS were older and a significantly higher proportion had CAC compared with those without ICAS. The proportion of subjects with CAC increased as the number of stenotic intracranial arteries increased from 0 to ≥3. When the OR for ICAS was analyzed with logistic regression analysis, CAC showed a significantly increased OR of 1.439 for ICAS after adjustment for confounding variables, which showed a significantly increased OR in the highest CACS (CACS>100). However, when logistic regression analysis was performed with presence of CAC as the dependent variable, the presence of ICAS did not show increased risk for CAC. The results of this study indicate the significance of the 2 assessment methods for atherosclerosis, ICAS and CAC in the prediction of atherosclerotic burden.

**Table 3. Comparison of the Parameters Between the Groups Without or With ICAS**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects Without ICAS (n=10,227, 96.9%)</th>
<th>Subjects With ICAS (n=323, 3.1%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43.2±8.8</td>
<td>45.5±10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex: male, %</td>
<td>8359 (81.7)</td>
<td>213 (65.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.5±3.1</td>
<td>24.1±3.1</td>
<td>0.049</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>115.6±13.1</td>
<td>118.5±12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>74.5±9.8</td>
<td>75.7±9.6</td>
<td>0.033</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dL</td>
<td>99.0±17.6</td>
<td>101.0±24.8</td>
<td>0.140</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>203.3±35.9</td>
<td>205.4±38.2</td>
<td>0.307</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>139.6±90.5</td>
<td>134.6±84.4</td>
<td>0.331</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>53.3±13.1</td>
<td>54.5±14.0</td>
<td>0.086</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>128.5±32.4</td>
<td>129.6±34.4</td>
<td>0.553</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.7±0.6</td>
<td>5.8±0.8</td>
<td>0.050</td>
</tr>
<tr>
<td>Ln(CACS+1)</td>
<td>0.56±1.4</td>
<td>0.94±1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proportion of subjects with history of diabetes mellitus, %</td>
<td>455 (4.4)</td>
<td>24 (7.4)</td>
<td>0.012</td>
</tr>
<tr>
<td>Proportion of subjects with history of hypertension, %</td>
<td>1786 (17.5)</td>
<td>100 (31.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proportion of subjects with history of ischemic stroke, %</td>
<td>22 (0.2)</td>
<td>8 (2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proportion of subjects with history of myocardial infarction, %</td>
<td>66 (0.6)</td>
<td>7 (2.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Proportion of subjects who has ever smoked, %*</td>
<td>5203 (50.9)</td>
<td>145 (44.9)</td>
<td>0.020</td>
</tr>
<tr>
<td>Proportion of subjects with CAC, %</td>
<td>1747 (17.1)</td>
<td>80 (24.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcification; CACS, coronary artery calcium score; HbA1c, glycohemoglobin; HDL-C, high-density lipoprotein cholesterol; ICAS, intracranial arterial stenosis; LDL-C, low-density lipoprotein cholesterol; and Ln(CACS), logarithmized form of coronary artery calcium score+1.

*Ever-smoker was defined as one who has ever smoked >5 packs of cigarettes during the life time.
ICAS is the process of atherosclerosis that affects large intracranial arteries. Interest in ICAS has increased in recent decades because of improved diagnostic methods. The prevalence of asymptomatic middle cerebral artery stenosis in Asian populations has been reported to be high, varying from 6.9% to 12.6%.\textsuperscript{6,5} Generally, the prevalence of ICAS among patients with significant ischemic events varied from 33% to 54% in Asians, which is relatively higher than that in non-Asians (8%–12.4%).\textsuperscript{5,6} ICAS is the cause of 30% to 50% of strokes in Asia and 8% to 10% in North America, making it one of the most common causes of stroke worldwide.\textsuperscript{10,11} However, the reason for the increased prevalence of ICAS in Asians is unknown.

In this study, 3.1% of the study participants were diagnosed with ICAS using TCD ultrasonography. In a study performed in 935 asymptomatic Korean adults who visited a stroke prevention clinic for diagnosis of ischemic stroke, 19.7% of the study population was diagnosed with ICAS by TCD ultrasonography.\textsuperscript{26} In another study performed in 5300 asymptomatic Chinese adults with a mean age of ≥52 years, 13.0% of the participants were diagnosed with ICAS by TCD ultrasonography.\textsuperscript{27} The prevalence of ICAS in our study is relatively lower than that in previously reported studies performed in Asians. We assume that this is because our study population was younger (43 years) than the previously reported study populations (52 years). In addition, our study population underwent yearly routine health examinations without any health concerns; therefore, there was less possibility of vascular abnormalities in our study population.

The optimal method for diagnosing ICAS and the clinical implications are still under debate. TCD ultrasonography is a noninvasive, safe, and cost-effective method for diagnosing ICAS. The positive predictive value of using TCD ultrasonography to detect stenosis varies in wide range from 55% to 100%, with a negative predictive value ranging from 83% to 97% compared with angiography.\textsuperscript{6} This wide range of predictive values attributes to different definitions of stenosis applied in different studies. The major disadvantages of TCD ultrasonography include operator dependence, the need for skilled interpretation, and inadequate bone windows. In a recent study performed in Chinese patients, the authors prospectively compared the diagnostic accuracy of TCD ultrasonography as an additional screening tool for ICAS with that of computed tomographic angiography in patients with acute ischemic stroke.\textsuperscript{15} They found that TCD ultrasonography demonstrated higher diagnostic accuracy than computed tomographic angiography, especially for middle cerebral artery, suggesting that TCD ultrasonography could be an alternative diagnostic tool to detect ICAS. Therefore, the results of our study using TCD ultrasonography could have more reliability according to the results of the previous study regarding the usage of TCD for diagnosing ICAS.\textsuperscript{15} In addition, greatest advantage of TCD in the setting like our study is the noninvasive character of the method without any radiation exposure.

As CAC is known to correlate well with global atherosclerotic burden, CAC could be considered a predictor for stroke. A recent report from the Heinz Nixdorf Recall study, which is one of the largest and strongest CAC cohorts, reported CACS to be an independent stroke predictor in the 8-year follow-up period.\textsuperscript{20} In another study performed in Koreans, 290 first-time ischemic stroke patients were matched with 580 reference control patients.\textsuperscript{28} They found that moderate-to-extensive CAC (CACS=100) was associated with ischemic stroke with an OR of 1.72. However, few studies have evaluated the direct association between ICAS and CAC.

In our study, subjects who had CAC showed significantly higher proportion of subjects with ICAS, although overall proportion is small. Conversely, the subjects who had ICAS showed significantly higher proportion of subjects with CAC compared with those who do not have ICAS. These results could indicate a higher risk for coronary artery disease in subjects with ICAS, as assessed by TCD ultrasonography, than in those without ICAS and vice versa. In addition, the proportion of subjects with ICAS significantly increased with the severity of CAC, as assessed by CACS, suggesting a correlation between the degree of CAC and ICAS. These results suggest that if CAC is present in an asymptomatic healthy subject, ICAS could be determined using TCD ultrasonography and vice versa. In addition, this risk for ICAS was found to increase with the severity of CAC.

Our study has several limitations. First, as this is a cross-sectional study, the exact cause–effect relationship cannot be determined from the results. Second, the proportion of subjects with ICAS in this study population was relatively small. Therefore, more specified analyses could not be performed and the reliability of the results could be low. However, this is because of the characteristics of the study participants, which included a relatively young age, in whom TCD ultrasonography and multidetector computed tomography was performed as a part of a routine health examination. Third, most of the participants in this study were men (>80%) because most of the employees in this medical screening cohort were men. Therefore, the results could have been biased because of the imbalance of sex. However, as the participants were general population mostly without any disease, the study results...
suggest the epidemiological data of normal population. Fourth, the reliability of TCD ultrasonography for ICAS diagnosis has to be validated further because few studies have been published using attesting to this. Despite these limitations, our study has strength in that we examined the relationship between ICAS and CAC in a young Asian population. Further prospective studies to actually observe the differences in the cardiovascular events in subjects who have ICAS and CAC are warranted.

Conclusions

We report the significant association of ICAS, as assessed by TCD ultrasonography, and CAC in a large Korean population via a cross-sectional study. In addition, we observed that the degree of TCD ultrasonography correlated well with the degree of CAC after adjustment for confounding factors. Future studies are needed to apply these results to a general population of a similar age and to establish preventive measures for cardiovascular events in this population.

Disclosures

None.

References

Increased Risk for Intracranial Arterial Stenosis in Subjects With Coronary Artery Calcification

Hyung-Geun Oh, Pil-Wook Chung and Eun-Jung Rhee

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Data Supplement (unedited) at:
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Supplemental Materials

Supplemental Methods

Participants

This cross-sectional study was part of the Kangbuk Samsung Health Study (KSHS), in which the subjects were the participants in a medical health checkup program at the Health Promotion Center of Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea.

The study was approved by the institutional review board (IRB) of Kangbuk Samsung Hospital (KBC13051), which exempted the requirement of informed consent as we only used deidentified data routinely collected during the health screening process.

The purpose of the medical health checkup program is to promote employees’ health through regular health checkups and allow early detection of diseases. Most of the examinees are employees and family members of various industrial companies from around the country. Their employers largely pay for the costs of the medical examinations and a considerable proportion of the examinees undergo examinations annually or biannually.

The initial study population included 10,614 subjects who participated in the medical checkup program from January 2010 to December 2012 for whom TCD ultrasonography and CACS data were available. We excluded 64 subjects with missing data or poor temporal windows. This exclusion resulted in a final study population of 10,550 subjects.

Anthropometric and Laboratory Measurements

Height and weight were measured twice and then averaged. The body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m). Blood pressure was measured using a standardized sphygmomanometer after 5 min of rest.

All subjects were examined after an overnight fast. The hexokinase method was used to test fasting glucose concentrations (Hitachi Modular D2400; Roche, Tokyo, Japan). An enzymatic calorimetric test was used to measure the total cholesterol and triglyceride concentrations. The selective inhibition method was used to measure the level of high-density lipoprotein cholesterol (HDL-C) and a homogeneous enzymatic calorimetric test was used to measure the level of low-density lipoprotein cholesterol (LDL-C).

The presence of diabetes mellitus was determined according to a self-questionnaire completed by the participants and classification based on the diagnostic criteria of the American Diabetes Association. Subjects were considered hypertensive if they were using anti-hypertensive medication, had a systolic blood pressure ≥140 mmHg, or had a diastolic blood pressure ≥90 mmHg. History for ischemic stroke or myocardial infarction was determined on the basis of the responses in the self-questionnaire. ‘Ever smoking’ was defined as the use of 5 packs of cigarettes during the subject’s lifetime.

Statistical Analyses
All data are presented as the mean and standard deviation, and were analyzed using SPSS Windows version 18.0 (SPSS Inc., Chicago, IL, USA). Student’s *t*-test was used to compare the mean values of the parameters between the subjects with and without CAC or ICAS. Comparison of the proportion of the subjects with and without CAC or ICAS was performed using the chi-square method. Logistic regression analysis was performed with CAC or ICAS as the dependent variable after adjustment for confounding factors. Significance was defined as *P* value of < 0.05.

References


**Supplemental Table I. Logistic regression analysis with CAC as the dependent variable after adjustment for confounding factors**

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds ratio*</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Upper</td>
<td>Lower</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of ICAS</td>
<td>1.270</td>
<td>0.922</td>
<td>1.749</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteries involved in ICAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>1.182</td>
<td>0.828</td>
<td>1.686</td>
</tr>
<tr>
<td>Distal internal carotid artery</td>
<td>0.820</td>
<td>0.280</td>
<td>2.400</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>1.921</td>
<td>0.187</td>
<td>19.756</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>3.586</td>
<td>1.439</td>
<td>8.938</td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>0.796</td>
<td>0.361</td>
<td>1.757</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, BMI, systolic blood pressure, total cholesterol, HbA1c, smoking and CVD history

CAC indicates coronary artery calcification; ICAS, intracranial atherosclerosis; BMI, body mass index; HbA1c, glycated hemoglobin; CVD, cerebrovascular disease