Predictors of Symptomatic and Asymptomatic Intracranial Atherosclerosis: What is Different and Why?

Bum Joon Kim¹, Keun-Sik Hong², Yong-Jin Cho², Ju-Hun Lee³, Ja-seong Koo⁴, Jong-Moo Park⁵, Dong-Wha Kang¹, Jong S. Kim¹, Seung-Hoon Lee⁶, Sun U. Kwon¹, on behalf of TOSS-2 investigators

¹Department of Neurology, Asan Medical Center, University of Ulsan, Seoul, Korea
²Department of Neurology, Ilsan Paik Hospital, Inje University, Ilsan, Korea
³Department of Neurology, Kangdong Sacred Heart Hospital, Seoul, Korea
⁴Department of Neurology, Seoul St. Mary's Hospital, Catholic University, Seoul, Korea
⁵Department of Neurology, Eulji General Hospital, Eulji University, Seoul, Korea
⁶Department of Neurology, Seoul National University Hospital, Seoul, Korea

Introduction

Intracranial atherosclerotic stenosis (ICAS) is a major cause of ischemic stroke, especially in Asian countries. The high rate of subsequent vascular events emphasizes the clinical importance of diagnosing symptomatic ICAS. A quarter of symptomatic ICAS patients have been found to have at least one concomitant condition of asymptomatic ICAS. In contrast to symptomatic ICAS, the risk of ischemic stroke secondary to asymptomatic ICAS is low and the long-term prognosis is benign. However, the rate of pro-
Regression of asymptomatic ICAS is considerable. Unfortunately, data describing the progression or regression of ICAS are scarce, and the pathomechanisms and/or predictors of symptomatic and asymptomatic ICAS have not been sufficiently investigated. In contrast, the clinical course and pathomechanisms of other forms of symptomatic atherosclerosis are well known. In the coronary arteries, silent plaque rupture increases the severity of stenosis, while abrupt episodes of rupture can cause acute progression of atherosclerosis. Coronary-type plaque rupture also plays an important role in the carotid arteries, and the process of plaque healing and remodeling after plaque rupture in symptomatic carotid arteries has been well described.

According to the results of our recent study, 'Trials of Cilostazol in Symptomatic intracranial arterial stenosis (TOSS)-2,' the progression or regression of symptomatic ICAS is frequently observed, even with a short period of seven months. We hypothesized that the pathomechanisms and predictors of the progression or regression of symptomatic ICAS differ from those of concomitant asymptomatic ICAS.

**Aim**

This analysis was performed to compare the course and predictors of symptomatic ICAS and coexisting asymptomatic ICAS. Additionally, as the recurrence of stroke is closely associated with the severity of atherosclerosis, identifying predictors of symptomatic ICAS may also be helpful for establishing strategies to prevent secondary ischemic stroke in this patient population.

**Methods**

**Study Design and Participants**

This study was a post-hoc analysis of the TOSS-2 trial (Unique identifier: NCT00130039). The details of the study design and results of the primary study have been published previously. In brief, in order to compare the efficacy of cilostazol (daily; 100 mg of aspirin and 200 mg of cilostazol) and clopidogrel (daily; 100 mg of aspirin and 75 mg of clopidogrel) in inhibiting the progression of ICAS, 457 acute ischemic stroke patients with symptomatic ICAS within two weeks after symptom onset were included. The patients' demographic characteristics and medical history regarding vascular risk factors were obtained at recruitment. Systolic and diastolic blood pressure measurements and various blood test parameters were obtained on the day of admission. Three-dimensional time-of-flight magnetic resonance angiography (MRA) was performed twice, first at baseline and seven months later, at each participating center. In order to prevent technical bias, baseline and follow-up MRI was performed using the same MRI scanner with identical MR parameters. All participants received the best medical treatment with aggressive risk factor control, including the appropriate use of statins. Written informed consent was provided by all patients or their legally authorized representatives. The trial protocol was approved by the ethics committees of all participating centers.

**Evaluation of the Progression of Atherosclerosis in the Intracranial Arteries**

According to the previously published TOSS grading system, the severity of ICAS was measured in the right and left middle cerebral arteries and basilar artery and classified as follows: normal (0), mild (1: signal reduction <50%), moderate (2: signal reduction >50%), severe (3: focal signal loss with a distal flow) or occlusion (4: sudden cutoff without a distal flow void). The MRA grade of the intracranial artery with an acute ischemic lesion in the pertinent vascular territory was used to assess the severity of symptomatic ICAS. If atherosclerotic stenosis was observed in more than one of the two remaining asymptomatic intracranial arteries, the mean MRA grade of the two asymptomatic arteries was used to determine the severity of asymptomatic ICAS. The patients were classified as exhibiting ‘progression,’ ‘regression’ or ‘no changes’ according to the change in the status of ICAS. Each patient was evaluated for worsening, improvements or no changes in the degree of stenosis on the follow-up examination. Depending on the changes, the course of ICAS was classified as being ‘favorable,’ defined as exhibiting a trend toward regression, or ‘unfavorable,’ defined as exhibiting a trend toward progression. Two reviewers blinded to the patients’ clinical information independently classified the degree of stenosis on MRA. Cases of discrepancies were resolved by consensus with a third investigator.

**Statistical Analysis**

The correlation between the changes in the status of symptomatic and asymptomatic ICAS was explored using the Spearman rank test, and the clinical, laboratory and radiologic variables were compared between the subjects with different degrees of change in symptomatic or asymptomatic ICAS. The linear-by-linear association model with the Chi-square statistic or contrast weighting ANOVA (analysis of variance) were used, as appropriate, for the evaluation. Concerning
Predictors of ICAS

receptor blockers [ARBs] and angiotensin-converting enzyme inhibitors and severity of asymptomatic ICAS). The statistical analyses were performed using the SPSS software program (version 17.0; Chicago, IL).

Results

Ultimately, a total of 409 patients completed the full analysis and were included in this post-hoc analysis. Among these patients, 250 had asymptomatic ICAS. At baseline, the severity of symptomatic ICAS was $2.0 \pm 0.8$, and the average MRA grade of stenosis for asymptomatic ICAS was $1.3 \pm 1.4$ (Fig. 1). Symptomatic ICAS regressed in 110 (27%) patients, did not change in 247 (60%) patients and progressed in 52 (13%) patients. The rate of progression or regression in asymptomatic ICAS was lower than that of symptomatic ICAS ($p=0.004$): regression in 38 (15%) cases, progression in 16 (6%) cases and no changes in 196 (78%) cases. The changes in atherosclerosis were the interaction between statins and clopidogrel, the proportion of patients on statin treatment was subanalyzed according to the type of concomitantly used antiplatelet agent. The changes in the status of ICAS were also explored according to the initial severity of ICAS. Univariate and multivariate analyses with ordinal regression modeling were used to determine independent predictors influencing the course of symptomatic and asymptomatic ICAS. The previously defined terms of a ‘favorable’ or ‘unfavorable’ course were used to describe the results of the trend and ordinal regression analyses. Variables with a $p$ value of $<0.20$ in the univariate analysis were entered into each multivariate model (model for symptomatic ICAS: sex, hypertension, fasting glucose, apolipoprotein B, high-density lipoprotein [HDL] cholesterol, type of antiplatelet agent, severity of symptomatic ICAS and severity of asymptomatic ICAS; model for asymptomatic ICAS: sex, the levels of fasting glucose and apolipoprotein A1, type of antiplatelet agent, use of angiotensin

Fig. 1. Initial severity and changes in the status of symptomatic and asymptomatic intracranial atherosclerotic stenosis (ICAS).

The distribution of the patients according to the initial severity (A and B) and changes in the status of ICAS (C and D). The mean MRA grade of the two asymptomatic ICAS scores was used to determine the initial severity of asymptomatic ICAS ($\mu$).

A

Initial severity of symptomatic ICAS

B

Initial severity of asymptomatic ICAS

C

Outcomes of symptomatic ICAS

D

Outcomes of asymptomatic ICAS

The interaction between statins and clopidogrel, the proportion of patients on statin treatment was subanalyzed according to the type of concomitantly used antiplatelet agent. The changes in the status of ICAS were also explored according to the initial severity of ICAS. Univariate and multivariate analyses with ordinal regression modeling were used to determine independent predictors influencing the course of symptomatic and asymptomatic ICAS. The previously defined terms of a ‘favorable’ or ‘unfavorable’ course were used to describe the results of the trend and ordinal regression analyses. Variables with a $p$ value of $<0.20$ in the univariate analysis were entered into each multivariate model (model for symptomatic ICAS: sex, hypertension, fasting glucose, apolipoprotein B, high-density lipoprotein [HDL] cholesterol, type of antiplatelet agent, severity of symptomatic ICAS and severity of asymptomatic ICAS; model for asymptomatic ICAS: sex, the levels of fasting glucose and apolipoprotein A1, type of antiplatelet agent, use of angiotensin

Fig. 1. Initial severity and changes in the status of symptomatic and asymptomatic intracranial atherosclerotic stenosis (ICAS).

The distribution of the patients according to the initial severity (A and B) and changes in the status of ICAS (C and D). The mean MRA grade of the two asymptomatic ICAS scores was used to determine the initial severity of asymptomatic ICAS ($\mu$).
much more dynamic in the patients with symptomatic ICAS, and the correlation between the changes in the status of symptomatic and the status of asymptomatic ICAS was low ($\rho = 0.084$; $p = 0.184$).

**Factors Associated with Symptomatic ICAS**

There were no differences in terms of the demographic or vascular risk factors between the three groups. A high level of HDL cholesterol was marginally associated with a favorable course of ICAS (regression: $45.1 \pm 12.7$ mg/dL; no change, $43.5 \pm 11.5$ mg/dL; progression, $41.0 \pm 11.9$ mg/dL; $p = 0.061$). The proportion of patients who used cilostazol was higher among those with a favorable course of symptomatic ICAS (regression: 55.5%; no change: 49.0%; progression: 38.5%; $p = 0.047$). Approximately 70% of the patients were treated with a statin during the trial, and the proportion of patients taking statins did not differ across the three groups. The severity of asymptomatic ICAS also did not differ between the three groups.
Table 2. Differences in the clinical, initial laboratory and imaging data according to the changes in the status of asymptomatic ICAS

|                     | Regression (n=38) | No change (n=196) | Progression (n=16) | p-value |
|---------------------|------------------|-------------------|--------------------|---------|
| Clinical data       |                  |                   |                    |         |
| Age (y)             | 66.8 ± 10.2      | 66.4 ± 11.2       | 66.5 ± 10.8        | 0.982   |
| Male                | 15 (39.5)        | 97 (49.5)         | 8 (50.0)           | 0.324   |
| Hypertension        | 31 (81.6)        | 151 (77.0)        | 12 (75.0)          | 0.522   |
| Diabetes            | 16 (42.1)        | 94 (59.4)         | 9 (56.3)           | 0.336   |
| Hyperlipidemia      | 24 (63.2)        | 91 (46.4)         | 11 (68.8)          | 0.597   |
| Smoking             | 19 (50.0)        | 79 (40.3)         | 5 (31.3)           | 0.165   |
| Cardiac disease     | 1 (2.6)          | 12 (6.1)          | 0 (0)              | 0.929   |
| Systolic pressure (mmHg) | 142 ± 23 | 143 ± 24          | 142 ± 31           | 0.910   |
| Diastolic pressure (mmHg) | 81 ± 11 | 82 ± 12           | 83 ± 12            | 0.477   |
| Laboratory data     |                  |                   |                    |         |
| WBC (×10³/mm³)      | 7.4 ± 2.4        | 7.6 ± 2.2         | 7.0 ± 2.1          | 0.751   |
| Hemoglobin (g/dL)   | 13.6 ± 1.5       | 13.8 ± 1.7        | 13.9 ± 2.2         | 0.541   |
| Platelets (×10³/mm³)| 241 ± 62         | 243 ± 58          | 261 ± 64           | 0.398   |
| Fasting glucose (mg/dL) | 132 ± 62 | 145 ± 70          | 190 ± 96           | 0.016   |
| Cholesterol (mg/dL) | 200 ± 51         | 193 ± 44          | 197 ± 34           | 0.577   |
| HDL cholesterol (mg/dL) | 42.6 ± 11.0 | 43.4 ± 11.4       | 42.7 ± 12.8        | 0.848   |
| LDL cholesterol (mg/dL) | 128 ± 46 | 120 ± 35          | 116 ± 29           | 0.217   |
| Apolipoprotein A1 (mg/dL) | 126 ± 29 | 123 ± 23          | 111 ± 25           | 0.116   |
| Apolipoprotein B (mg/dL) | 75 ± 26 | 87 ± 66           | 83 ± 28            | 0.413   |
| C-reactive protein (mg/dL) | 0.29 ± 0.38 | 0.39 ± 0.85       | 0.41 ± 0.33        | 0.529   |
| Current medications |                  |                   |                    |         |
| Cilostazol          | 24 (63.2)        | 100 (51.0)        | 7 (43.8)           | 0.130   |
| ARB                 | 21 (55.3)        | 74 (37.9)         | 5 (31.3)           | 0.043   |
| ACEI                | 10 (26.3)        | 37 (19.0)         | 2 (12.5)           | 0.202   |
| CCB                 | 20 (52.6)        | 97 (49.7)         | 8 (50.0)           | 0.791   |
| Statin              | 31 (81.6)        | 139 (71.3)        | 14 (87.5)          | 0.815   |
| With cilostazol *   | 21 (87.5)        | 68 (68.0)         | 5 (71.4)           | 0.117   |
| With clopidogrel ** | 10 (71.4)        | 71 (74.7)         | 9 (100)            | 0.168   |
| Imaging data        |                  |                   |                    |         |
| Severity of symptomatic ICAS | 2.1 ± 1.0 | 2.1 ± 0.8        | 1.8 ± 0.8          | 0.226   |
| Severity of asymptomatic ICAS | 1.4 ± 0.5 | 1.0 ± 0.5        | 1.1 ± 0.7          | 0.002   |

The results are expressed as the number (column %) or mean ± standard deviation.

*Represents the proportion of subjects among the 202 subjects randomized to receive cilostazol
**Represents the proportion of subjects among the 207 subjects randomized to receive clopidogrel

WBC: white blood cell; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ARB: angiotensin-receptor blocker; ACEI: angiotensin-converting enzyme inhibitor; CCB: calcium-channel blocker; ICAS: intracranial atherosclerosis.

However, a high severity of symptomatic ICAS was found to be associated with a favorable course of symptomatic ICAS (regression: 2.4 ± 0.8; no change: 1.9 ± 0.9; progression: 1.9 ± 0.8; p < 0.001, Table 1). In addition, the proportion of patients with symptomatic ICAS regression increased as the severity of baseline stenosis of symptomatic ICAS increased (p < 0.001; Fig. 1).

Factors Associated with Asymptomatic ICAS

The demographic characteristics and vascular risk factors did not differ between the three groups. A low fasting glucose level and the use of ARB were found to be associated with a favorable course of asymptomatic ICAS (p = 0.016, p = 0.043; respectively). A high severity of asymptomatic ICAS was also found to be associated with a favorable course of ICAS (p = 0.002; Table 2), and the proportion of patients with asymptomatic ICAS regression increased as the initial severity of
In the present study, we investigated factors predicting a favorable course of symptomatic or asymptomatic intracranial arteries. Our results demonstrated that symptomatic ICAS changed more dynamically than asymptomatic ICAS, and the courses of these conditions were independent of each other. The predictors of symptomatic and asymptomatic ICAS were slightly different. For example, a favorable course of symptomatic ICAS was strongly predicted by a high HDL cholesterol level and the use of cilostazol, while the use of ARBs and a low fasting glucose level were independent predictors of a favorable course of asymptomatic ICAS. Interestingly, favorable courses of both symptomatic and asymptomatic ICAS were strongly predicted by the degree of stenosis in each artery at

**Independent Predictors of Symptomatic and Asymptomatic ICAS**

For symptomatic ICAS, the use of cilostazol, a high HDL cholesterol level and high initial severity of stenosis strongly predicted a favorable course, after adjusting for potential confounders (p=0.038, p=0.005 and p<0.001; respectively; **Table 3**). For asymptomatic ICAS, a high severity of asymptomatic ICAS, the use of ARBs and a low fasting glucose level were independent predictors of a favorable course according to the results of the multivariate analysis (p<0.001, p=0.011 and p=0.007, respectively; **Table 4**).

**Discussion**

In the present study, we investigated factors predicting a favorable course of symptomatic or asymptomatic intracranial arteries. Our results demonstrated that symptomatic ICAS changed more dynamically than asymptomatic ICAS, and the courses of these conditions were independent of each other. The predictors of symptomatic and asymptomatic ICAS were slightly different. For example, a favorable course of symptomatic ICAS was strongly predicted by a high HDL cholesterol level and the use of cilostazol, while the use of ARBs and a low fasting glucose level were independent predictors of a favorable course of asymptomatic ICAS. Interestingly, favorable courses of both symptomatic and asymptomatic ICAS were strongly predicted by the degree of stenosis in each artery at
Predictors of ICAS

In this study, symptomatic ICAS was associated with a more advanced stage of atherosclerosis and a higher severity of stenosis. The presence of a larger lipid core and reverse cholesterol transport by HDL cholesterol can explain the correlation between the initial HDL cholesterol level and the course of atherosclerosis\(^\text{19}\). Previously, a high serum HDL cholesterol level was reported to be associated with the transformation of plaque into areas of higher echogenicity representing a decreased lipid content and reduced severity of atherosclerosis\(^\text{20}\). Furthermore, a randomized controlled trial demonstrated that the administration of short-term reconstituted HDL infusion therapy significantly improves the plaque characterization index\(^\text{21}\). In addition to its cholesterol efflux function, HDL cholesterol possesses anti-inflammatory and positive vascular remodeling properties that contribute to baseline.

The predictors of asymptomatic ICAS identified in this study are consistent with known predictors of atherosclerosis. A low fasting blood glucose level and the use of ARBs have been reported to be negatively associated with the severity and progression of atherosclerosis in the coronary\(^\text{13, 14}\) and carotid arteries\(^\text{15, 16}\). In the present study, asymptomatic ICAS represented less severe stenosis and an earlier stage of atherosclerosis than symptomatic ICAS. These two factors - fasting blood glucose and angiotensin use - are both closely associated with endothelial dysfunction, which exacerbates the severity of atherosclerosis\(^\text{17, 18}\). However, the predictors of symptomatic ICAS differed from those of asymptomatic ICAS in this study.

A high HDL cholesterol level was found to independently predict a favorable course of symptomatic ICAS. In this study, symptomatic ICAS was associated with a more advanced stage of atherosclerosis and a higher severity of stenosis. The presence of a larger lipid core and reverse cholesterol transport by HDL cholesterol can explain the correlation between the initial HDL cholesterol level and the course of atherosclerosis\(^\text{19}\). Previously, a high serum HDL cholesterol level was reported to be associated with the transformation of plaque into areas of higher echogenicity representing a decreased lipid content and reduced severity of atherosclerosis\(^\text{20}\). Furthermore, a randomized controlled trial demonstrated that the administration of short-term reconstituted HDL infusion therapy significantly improves the plaque characterization index\(^\text{21}\). In addition to its cholesterol efflux function, HDL cholesterol possesses anti-inflammatory and positive vascular remodeling properties that contribute to

### Table 4. Independent predictors of the course of asymptomatic ICAS

| Predictor                      | Estimate | p-value | Adjusted Estimate | Adjusted p-value |
|--------------------------------|----------|---------|------------------|-----------------|
| Age                            | -0.005   | 0.710   | -                | -               |
| Male                           | 0.382    | 0.185   | 0.088            | 0.787           |
| Hypertension                   | 0.322    | 0.321   | -                | -               |
| Diabetes                       | 0.221    | 0.448   | -                | -               |
| Hyperlipidemia                 | -0.221   | 0.440   | -                | -               |
| Smoking                        | -0.210   | 0.465   | -                | -               |
| Previous stroke history        | -0.281   | 0.378   | -                | -               |
| Cardiac disease                | -0.04    | 0.938   | -                | -               |
| Systolic BP                    | <0.001   | 0.930   | -                | -               |
| Diastolic BP                   | 0.009    | 0.494   | -                | -               |
| WBC                            | -0.012   | 0.851   | -                | -               |
| Hemoglobin                     | 0.093    | 0.271   | -                | -               |
| Platelet                       | 0.001    | 0.541   | -                | -               |
| Fasting glucose                | 0.005    | 0.018   | 0.006            | 0.007           |
| Total cholesterol              | -0.002   | 0.498   | -                | -               |
| LDL cholesterol                | -0.004   | 0.302   | -                | -               |
| HDL cholesterol                | -0.001   | 0.927   | -                | -               |
| C-reactive protein             | 0.202    | 0.277   | -                | -               |
| Apolipoprotein A1              | -0.012   | 0.054   | -0.011           | 0.076           |
| Apolipoprotein B               | 0.002    | 0.426   | -                | -               |
| Cilostazol                     | -0.593   | 0.044   | -0.439           | 0.177           |
| ARB                            | -0.713   | 0.017   | -0.870           | 0.011           |
| ACEI                           | -0.470   | 0.192   | -0.434           | 0.889           |
| CCB                            | -0.106   | 0.712   | -                | -               |
| Statin                         | -0.086   | 0.781   | -                | -               |
| Severity of symptomatic ICAS   | -0.212   | 0.212   | -                | -               |
| Severity of asymptomatic ICAS  | -0.501   | <0.001  | -0.544           | <0.001          |

The adjusted estimate and p-value represent the results of the multivariate analysis.

WBC: white blood cell; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ARB: angiotensin-receptor blocker; ACEI: angiotensin-converting enzyme inhibitor; CCB: calcium-channel blocker; ICAS: intracranial atherosclerosis.
the stabilization of ruptured plaque and may help heal areas of plaque. 

Cilostazol, which also exhibits pleiotropic effects, including anti-inflammatory properties, and influences vascular smooth muscle cell differentiation, is protective against an unfavorable course of ICAS. In the present study, the degree of atherosclerosis changed more dynamically in the patients with symptomatic intracranial arteries than in those with asymptomatic ICAS. As plaque rupture and healing is associated with abrupt changes in stenosis, this may be a major pathomechanism of symptomatic ICAS progression and/or regression. However, the exact mechanisms underlying the rapid progression or regression of symptomatic ICAS should be confirmed in further studies using advanced MRI techniques.

Based on the results of previous trials, treatment with statins and changes in lipid profiles are protective against the progression of atherosclerosis. In the current study, the participants received intensive medical treatment with antiplatelets and lipid-lowering agents. Only subjects with an unusually low low-density lipoprotein cholesterol level were excluded from receiving lipid-lowering agents, and as many as 70% of the enrolled subjects received statin therapy. Therefore, a high proportion of the patients with symptomatic ICAS, and even asymptomatic ICAS, demonstrated improved atherosclerosis. However, the antiatherogenic effects of statins may have been statistically underestimated, which may have contributed to the failure of statins to demonstrate a predictive value for improving ICAS. Intensive medical treatment with the appropriate use of statins and antiplatelet agents is the standard regimen for ICAS. Therefore, our results identified independent predictors of symptomatic and asymptomatic ICAS despite the use of intensive medical treatment, which represents recent real-world clinical practice.

In contrast to our results, the progression of symptomatic ICAS was found to be predicted by a high degree of baseline stenosis in a former study. In that study, less than 10% of the patients had more than a moderate degree of stenosis, and more than half were not treated with antiplatelet agents. However, based on another study of subjects on appropriate antiplatelet treatment, ICAS demonstrated more regression in symptomatic and severely stenotic vessels. Therefore, providing appropriate antiplatelet treatment is important for managing symptomatic ICAS, especially in severe cases. In addition, symptomatic ICAS responds dynamically and demonstrates a relatively good clinical outcome following intensive medical treatment, compared with the high progression rate of severe extracranial atherosclerosis after medical treatment. In the present study, a higher initial severity of ICAS was found to independently predict more preferable changes in the severity of atherosclerosis in both symptomatic and asymptomatic ICAS patients. Therefore, although the initial degree of symptomatic ICAS is severe, there remains the possibility of regression following intensive medical treatment with the administration of appropriate antiplatelet agents and risk factor control.

We investigated predictors of changes in the severity of atherosclerosis in intracranial arteries. Therefore, risk factors associated with clinical events, such as ischemic stroke, were not analyzed. Severe stenosis induces plaque rupture and distal embolization and reduces the washout of emboli. These alterations in hemodynamics induced by severe stenosis increase the risk of ischemic stroke recurrence. Although severe stenosis itself carries a higher risk of stroke recurrence, it may also regress with intensive medical treatment, even within a relatively short period of several months. Considering the fact that ischemic events are strongly correlated with the severity of ICAS, the clinical implications of ICAS regression may be carefully extended.

There are some other noteworthy limitations to this study. First, unlike that observed in the internal carotid artery, it is difficult to determine the pathology of ICAS or observe changes in the content of plaque using ultrasonography. Therefore, the pathomechanisms underlying symptomatic ICAS progression or regression were inferred from the predictors of symptomatic ICAS. Second, the follow-up period was only seven months after the initial ischemic stroke, and the use of a longer follow-up period may have strengthened our results. However, considering the dynamic changes observed in the patients with symptomatic ICAS, conducting frequent short-term follow-up evaluations of the ICAS status may be valuable. Third, because this study focused on the initial predictors of ICAS changes, follow-up laboratory data were not the primary concern. The variables and changes in the follow-up laboratory data were not significantly different between the three groups. Fourth, as the severity of stenosis was not blinded, the management strategies may have differed according to the initial severity of ICAS. However, there were no differences in the use of concomitant medications or changes in the laboratory results according to the initial severity of ICAS.
Conclusion

The changes in symptomatic ICAS are more dynamic than those observed in asymptomatic ICAS. Furthermore, the courses of symptomatic and asymptomatic ICAS are independent of each other, and the predictors of these conditions also differ. The predictors of symptomatic ICAS may reflect the high content of the lipid core and the presence of plaque rupture or the remodeling process in patients with symptomatic ICAS. The use of targeted medical treatment of symptomatic ICAS based on the underlying pathophysiology may help to improve the outcomes of symptomatic ICAS patients. In addition, considering that a high level of severity of baseline stenosis independently predicts preferable changes, the decision to apply interventional therapy, such as angioplasty or stenting, should not be determined based simply on the severity of symptomatic ICAS.

Acknowledgement

We would like to thank all TOSS-2 investigators for their devotion to the TOSS-2 study. Because some investigators were omitted from the previous article, we would like to introduce the investigators of the TOSS-2 trial.

Investigators of the TOSS-2 Study

Sun U. Kwon, MD1; Keun-Sik Hong, MD2; Dong-Wha Kang, MD3; Jong-Moo Park, MD3; Ju-Hun Lee, MD3; Yong-Jin Cho, MD2; Kyung-Ho Yu, MD3; Ja-Seong Koo, MD4; KS Lawrence Wong, MD5; Vincent C Mok, MD6; Seung-Hoon Lee, MD7; Kyung Bok Lee8; MD; Dong-Eog Kim, MD9; Sang-Wook Jeong, MD10; Hee-Joon Bae, MD10; Byung-Chul Lee, MD3; Moon-Ku Han, MD8; Jung-Ho Rha, MD11; Hahn Young Kim, MD12; Vincent C Mok, MD7; Yong-Seok Lee, MD8; Gyeong-Moon Kim, MD13; Nijasri Charinnaong Suwanwela, MD14; Sung-Cheol Yun, PhD15; Jose C. Navarro, MD16; Maria Cristina San Jose, MD17; Disya Ratanakorn, MD18; Niphon Poungvarin, MD19; Raymond Cheung, MD20; Jong S. Kim, MD1

1 Asan Medical Center, University of Ulsan, Seoul, Korea
2 Ilsan Paik Hospital, Inje University, Ilsan, Korea
3 Eulji University, Eulji University, Seoul, Korea
4 Kangdong Sacred Heart Hospital, Seoul, Korea
5 Hallym University Sacred Heart Hospital, Anyang, Korea
6 Seoul St Mary’s Hospital, Catholic University, Seoul, Korea
7 Chinese University of Hong Kong, Hongkong, China
8 Seoul National University Hospital, Seoul, Korea
9 Soonchunhyang University Hospital, Seoul, Korea
10 Dongguk University Ilsan Hospital, Ilsan, Korea
11 Inha University Hospital, Incheon, Korea
12 Konkuk University, Seoul, Korea
13 Samsung Medical Center, Sungkyunkwan University, Seoul, Korea
14 Chulalongkorn University, Bangkok, Thailand
15 Department of Clinical Epidemiology and Biostatistics, University of Ulsan, Seoul, Korea
16 University of Santo Tomas Hospital, Manila, Philippines
17 UP-Philippine General Hospital, Manila, Philippines
18 Division of Neurology, Mahidol University, Ramathibodi Hospital, Bangkok, Thailand
19 Mahidol University, Siriraj Hospital, Bangkok, Thailand
20 Queen Mary Hospital, Hong Kong, China

Sources of Funding

This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI10C2020).

Conflicts of Interest

Disclosures

Korea Otsuka Pharmaceutical (KOP) Company, Korea Otsuka International Asia and Arab Co Ltd. provided financial support for the TOSS-2 study. However, these institutions played no role in protocol development, data collection, analysis or manuscript preparation in the current study.

Dr. B.J. Kim, Dr. K.S. Hong, Dr. Y.J. Cho, Dr. J.H. Lee, Dr. J.S. Koo, Dr. J.M. Park, Dr. D.W. Kang, Dr. J.S. Kim, Dr. S.H. Lee and Dr. S.U. Kwon have nothing to disclose individually.

References

1) Mazighi M, Tanasescu R, Ducrocq X, Vicaut E, Bracard S, Houdart E, Woeimant F: Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. Neurology, 2006; 66: 1187-1191
2) Nahab F, Cotsonis G, Lynn M, Feldmann E, Chaturvedi S, Hemphill JC, Zweifler R, Johnston K, Bonovich D, Kasner S, Chimowitz M, Group WS: Prevalence and prognosis of coexistent asymptomatic intracranial stenosis. Stroke, 2008; 39: 1039-1041
3) Kern R, Steinke W, Daffertshofer M, Prager R, Hennerici M: Stroke recurrences in patients with symptomatic vs asymptomatic middle cerebral artery disease. Neurology, 2005; 65: 859-864
4) Kremer C, Schaettin T, Georgiadis D, Baumgartner RW: Prognosis of asymptomatic stenosis of the middle cerebral artery. J Neurol Neurosurg Psychiatry, 2004; 75: 1300-1303
5) Qureshi AI, Caplan LR: Intracranial atherosclerosis. Lancet, 2013;
6) Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, Virmani R: Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation, 2001; 103: 934-940
7) Falk E, Shah PK, Fuster V: Coronary plaque disruption. Circulation, 1995; 92: 657-671
8) Carr S, Farb A, Pearce WH, Virmani R, Yao JS: Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. J Vasc Surg, 1996; 23: 755-765; discussion 765-756
9) Martinez-Sanchez P, Fernandez-Dominguez J, Ruiz-Ares G, Fuentes B, Alexandrov AV, Diez-Tejedor E: Changes in carotid plaque echogenicity with time since the stroke onset: an early marker of plaque remodeling? Ultrasound Med Biol, 2012; 38: 231-237
10) Teng Z, Degnan AJ, Sadat U, Wang F, Young VE, Graves MJ, Chen S, Gillard JH: Characterization of healing following atherosclerotic carotid plaque rupture in acutely symptomatic patients: an exploratory study using in vivo cardiovascular magnetic resonance. J Cardiovasc Magn Reson, 2011; 13: 64
11) Kwon SU, Hong KS, Kang DW, Park JM, Lee JH, Cho YJ, Yu KH, Koo JS, Wong KS, Lee SH, Lee KB, Kim DE, Jeong SW, Bae HJ, Lee BC, Han MK, Rha JH, Kim HY, Mok VC, Lee YS, Kim GM, Suwanwela NC, Yun SC, Nah HW, Kim JS: Efficacy and safety of combination antiplatelet therapies in patients with symptomatic intracranial atherosclerotic stenosis. Stroke, 2011; 42: 2883-2890
12) Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Benesch CG, Sila CA, Jovin TG, Romano JG, Cloft HJ, Warfarin Aspirin Symptomatic Intracranial Disease Trial I: Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation, 2006; 113: 555-563
13) Berry C, Noble S, Gregoire JC, Ibrahim R, Levesque S, Lavoie MA, L’Allier PL, Tardif JC: Glycaemic status influences the nature and severity of coronary artery disease. Diabetologia, 2010; 53: 652-658
14) Hirohata A, Yamamoto K, Miyoshi T, Hatanaka K, Hirohata S, Yamawaki H, Komatsubara I, Murakami M, Hirose E, Sato S, Ohkawa K, Ishizawa M, Yamaji H, Kawamura H, Kusachi S, Murakami T; Hina K, Ohe T: Impact of olmesartan on progression of coronary atherosclerosis a serial volumetric intravascular ultrasound analysis from the OLIIVUS (impact of Olmesarten on progression of coronary atherosclerosis: evaluation by intravascular ultrasound) trial. J Am Coll Cardiol, 2010; 55: 976-982
15) Folsom AR, Eckfeldt JH, Weitzman S, Ma J, Chambless LE, Barnes RW, Cran KB, Hutchinson RG: Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Stroke, 1994; 25: 66-73
16) Stumpe KO, Agabiti-Rosei E, Zielinski T, Schremmer D, Schulze J, Læsø P, Schandor P, Ludvig M, investigators Ms: Carotid intima-media thickness and plaque volume changes following 2-year angiotensin II-receptor blockade. The Multicentre Olmesartan atherosclerosis Regression Evaluation (MORE) study. Ther Adv Cardiovasc Dis, 2007; 1: 97-106
17) Hink U, Li H, Mollnau H, Oelze M, Mathies E, Hartmann M, Skatchkov M, Thais F, Stahl RA, Warnholtz A, Meineitz T, Friendling K, Harrison DG, Forstermann U, Munzel T: Mechanisms underlying endothelial dysfunction in diabetes mellitus. Circ Res, 2001; 88: E14-22
18) Kishi T, Hirooka Y, Konno S, Sunagawa K: Angiotensin II receptor blockers improve endothelial dysfunction associated with sympathetic hyperactivity in metabolic syndrome. J Hypertens, 2012; 30: 1646-1655
19) Lewis GF, Rader DJ: New insights into the regulation of HDL metabolism and reverse cholesterol transport. Circ Res, 2005; 96: 1221-1232
20) Johnsen SH, Mathiesen EB, Fosse E, Joakimsen O, Stensland-Bugge E, Njolstad I, Arnesen E: Elevated high-density lipoprotein cholesterol levels are protective against plaque progression: a follow-up study of 1952 persons with carotid atherosclerosis the Tromso study. Circulation, 2005; 112: 498-504
21) Tardif JC, Gregoire J, L’Allier PL, Ibrahim R, Lesperance J, Heinonen TM, Koutz S, Berry C, Basser R, Lavoie MA, Guertin MC, Rodes-Cabau J. Effect of r HDLoA-S, Efficacy I: Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA, 2007; 297: 1675-1682
22) Sviridov D, Mukhamedova N, Remaley AT, Chin-Dusting J, Nestel P: Antiatherogenic functionality of high density lipoprotein: how much versus how good. J Atheroscler Thromb, 2008; 15: 52-62
23) Taylor AJ, Burke AP, Farb A, Yousef P, Malcom GT, Smialek J, Virmani R: Arterial remodeling in the left coronary system: the role of high-density lipoprotein cholesterol. J Am Coll Cardiol, 1999; 34: 760-767
24) Takase H, Hashimoto A, Okutsu R, Hirose Y, Ito H, Imaizumi T, Miyakoda G, Mori T: Anti-atherosclerotic effect of cilostazol in apolipoprotein-E knockout mice. Arzneimittelforschung, 2007; 57: 185-191
25) Chen WJ, Chen YH, Lin KH, Ting CH, Yeh YH: Cilostazol promotes vascular smooth muscle cells differentiation through the cAMP response element-binding protein-dependent pathway. Arterioscler Thromb Vasc Biol, 2011; 31: 2106-2113
26) Kang S, Wu Y, Li X: Effects of statin therapy on the progression of carotid atherosclerosis: a systematic review and meta-analysis. Atherosclerosis, 2004; 177: 433-442
27) Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, Janis LS, Lutsep HL, Barnwell SL,
Waters MF, Hoh BL, Hourihane JM, Levy EI, Alexandrov AV, Harrigan MR, Chiu D, Klucznik RP, Clark JM, McDougall CG, Johnson MD, Pride GL Jr, Torbey MT, Zaidat OO, Rumboldt Z, Cloft HJ Investigators ST: Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med, 2011; 365: 993-1003

28) Shimizu K, Shimomura K, Tokuyama Y, Sakurai K, Isahaya K, Takaishi S, Kato B, Usuki N, Shimizu T, Yamada K, Hasegawa Y: Association between Inflammatory Biomarkers and Progression of Intracranial Large Artery Stenosis after Ischemic Stroke. J Stroke Cerebrovasc Dis, 2013; 22: 211-217

29) Yamada K, Fujimoto Y: Efficacy of cilostazol for intracranial arterial stenosis evaluated by digital subtraction angiography/magnetic resonance angiography. Adv Ther, 2011; 28: 866-878

30) Paciaroni M, Eliasziw M, Sharpe BL, Kappelle LJ, Chaturvedi S, Meldrum H, Barnett HJ: Long-term clinical and angiographic outcomes in symptomatic patients with 70% to 99% carotid artery stenosis. Stroke, 2000; 31: 2037-2042
### Supplementary Table 1
Follow-up laboratory data and changes in the laboratory data after seven months according to the changes in the status of ICAS

|                     | Regression ($n=110$) | No change ($n=247$) | Progression ($n=52$) | $p$-value |
|---------------------|----------------------|---------------------|----------------------|-----------|
| **Follow-up laboratory data** |                      |                     |                      |           |
| Fasting glucose     | 117 (39)             | 115 (40)            | 118 (44)             | 0.99      |
| Cholesterol         | 160 (33)             | 163 (38)            | 167 (37)             | 0.31      |
| HDL-C               | 50 (14)              | 49 (12)             | 46 (12)              | 0.08      |
| LDL-C               | 92 (30)              | 95 (33)             | 99 (33)              | 0.24      |
| Apo A1              | 130 (27)             | 136 (26)            | 133 (27)             | 0.56      |
| Apo B               | 73 (20)              | 75 (23)             | 81 (24)              | 0.03      |
| CRP                 | 0.34 (1.00)          | 0.23 (0.42)         | 0.48 (1.81)          | 0.37      |
| **Changes of laboratory data** |                      |                     |                      |           |
| Fasting glucose     | -21 (57)             | -28 (67)            | -10 (45)             | 0.35      |
| Cholesterol         | -35 (46)             | -28 (54)            | -22 (45)             | 0.16      |
| HDL-C               | 5.0 (11.2)           | 6.2 (11.3)          | 4.8 ± (11.0)         | 0.94      |
| LDL-C               | -31 (40)             | -23 (45)            | -20 (40)             | 0.17      |
| Apo A1              | 10 (24)              | 14 (25)             | 12 (31)              | 0.18      |
| Apo B               | -12 (25)             | -5 (28)             | -19 (127)            | 0.68      |
| CRP                 | -0.04 (1.29)         | -0.16 (0.83)        | 0.03 (2.10)          | 0.43      |

The results are expressed as the mean (standard deviation; mg/dL).
HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, Apo: apolipoprotein, CRP: C-reactive protein

### Supplementary Table 2
Use of concomitant medications according to the severity of ICAS

| Initial severity of ICAS (TOSS grading) | 0   | 1   | 2   | 3   | 4   | $p$  |
|-----------------------------------------|-----|-----|-----|-----|-----|------|
| Cilostazol                              | 1   | 62  | 76  | 59  | 4   | 0.28 |
| Statin                                  | 1   | 95  | 97  | 88  | 3   | 0.86 |
| ACEI                                    | 0   | 24  | 26  | 21  | 1   | 0.93 |
| ARB                                     | 2   | 49  | 50  | 52  | 3   | 0.32 |
| CCB                                     | 2   | 57  | 70  | 56  | 2   | 0.33 |

The results are expressed as the number (% column).
ICAS: intracranial atherosclerotic stenosis, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blocker, CCB: calcium-channel blocker
Supplementary Table 3
Blood pressure and changes in the laboratory results according to the severity of ICAS

| Initial severity of ICAS (TOSS grading) | 0       | 1       | 2       | 3       | 4       | p       |
|-----------------------------------------|---------|---------|---------|---------|---------|---------|
| Systolic BP                             | 160 ± 42| 143 ± 21| 142 ± 27| 138 ± 20| 147 ± 17| 0.30    |
| Diastolic BP                            | 85 ± 8  | 82 ± 10 | 82 ± 13 | 81 ± 10 | 84 ± 6  | 0.90    |
| Δ glucose                               | −56 ± 88| −26 ± 69| −30 ± 63| −14 ± 54| −20 ± 72| 0.30    |
| Δ cholesterol                           | 24 ± 89 | −31 ± 50| −30 ± 50| −24 ± 52| −47 ± 57| 0.41    |
| Δ LDL-C                                 | −9 ± 25 | −27 ± 45| −26 ± 40| −21 ± 45| −36 ± 35| 0.72    |
| Δ HDL-C                                 | −2 ± 16 | 5 ± 10  | 5 ± 11  | 8 ± 13  | 3 ± 5   | 0.20    |
| Δ CRP                                   | −0.4 ± 0.1| −0.1 ± 0.6| −0.02 ± 1.3| −0.03 ± 1.5| −0.9 ± 2.1| 0.65    |

The results are expressed as the number (% column).

ICAS: intracranial atherosclerotic stenosis, BP: blood pressure, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, CRP: C-reactive protein.