JoS JOURNAL OF STROKE

Journal of Stroke 2026;28(2):330-333
https://doi.org/10.5853/jos.2025.05652

Letter to the Editor

Impact of Low-Density Lipoprotein Cholesterol Levels on Atherosclerotic Vascular Changes: Analysis of Korean Treat Stroke to Target Trial

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Dear Sir:

The treat stroke to target (TST) trial demonstrated that achieving a lower low-density lipoprotein cholesterol (LDL-C) target (<70 mg/dL, low target [LT]) significantly reduced the risk of major cardio-cerebrovascular events compared with a higher target (90–110 mg/dL, high target [HT]).[1] A subsequent analysis of the Korean TST cohort showed that the LT strategy was particularly effective in preventing recurrent strokes among patients with symptomatic extracranial atherosclerosis (ECAS), but not in those with intracranial atherosclerosis (ICAS).[2] However, whether LT and HT strategies differ in terms of the imaging outcome (progression or regression) of ICAS and ECAS remains unknown.

We performed an additional analysis using vascular imaging data from Korean patients who underwent TST to address this. Between May 2015 and February 2021, 712 patients were recruited, 220 of whom underwent follow-up magnetic resonance angiography (MRA) at the physician's discretion. This is partly because this was a multicenter study and partly because this aspect was excluded from the initial design of the main TST; the characteristics of magnetic resonance imaging (MRI) used were heterogeneous: 1.5 T or 3.0 T scanners, including Siemens, GE, and Philips systems. Although specific acquisition parameters (such as repetition time, echo time, and flip angle) varied among institutions, each center followed standardized clinical protocols. The same modality, either time-of-flight MRA or contrast-enhanced MRA (CE-MRA), was used for both the baseline and follow-up scans. The most recent scan was used as the second dataset in patients who underwent multiple scans. The median follow-up interval was 2 years. Details of the TST have been described in a previous study,[1] and the ethics committees of all participating centers approved the protocol.

Investigators from each center who were blinded to the clinical information independently classified the degree of arterial

stenosis on MRA. The severity was categorized into four grades—0, no stenosis; 1, stenosis <50%; 2, stenosis of 50%–99%; and 3, severe or occlusion (focal signal loss with the relevant artery)[3,4]—for both the ICAS (middle cerebral artery, anterior cerebral artery [ACA], intracranial internal carotid artery, basilar artery, intracranial vertebral artery [VA], and posterior cerebral artery) and ECAS (proximal internal carotid artery and extracranial vertebral artery).[4] We measured the degree of stenosis across both ICAS and ECAS vessels to quantify the changes in total atherosclerotic burden. The total burden was calculated by subtracting the baseline score from the final follow-up score. Consequently, "progression" was defined as a positive net increase in the aggregate score, while "regression" was defined as a net decrease.[3] In cases where a patient exhibited simultaneous worsening in one vessel and improvement in another, the final classification was determined using the net mathematical sum. We also categorized patients into those with symptomatic ICAS (ischemic stroke ipsilateral to the ICAS) and those with symptomatic ECAS (ischemic stroke ipsilateral to the ECAS) and compared the vessel changes between these two groups.

Baseline characteristics were compared using the chi-square test, Fisher's exact test, Student's t-test, or Mann–Whitney U test. Factors associated with changes in ICAS and ECAS were analyzed using the Cox proportional hazards model, with the time interval between the baseline and follow-up MRA treated as the time-to-event variable. The results are presented as hazard ratios with 95% confidence intervals. Interaction analysis was used to assess whether the effect of the LDL-C target on stenosis change differed between the ICAS and ECAS groups. IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) was used for all analyses. Statistical significance was set at $P<0.05$.

We compared baseline characteristics between the follow-up (n=220) and non-follow-up (n=492) groups (Supplementary Table 1). No significant differences were observed between the groups except for hypertension and stroke history. Additionally, the prevalence of symptomatic stenosis was higher in the follow-up group than that in the non-follow-up group (71.8% vs. 62.4%, $P=0.015$).

Of the 220 patients included, 120 were in the LT group, and 100 were in the HT group. The mean age was 61±10 years, and 153 patients (69.5%) were male. Baseline patient characteristics are shown in Table 1. Age, sex, and medical comorbidities were similar between the two groups. Overall, no significant differences in stenosis severity changes were observed between the LT and HT groups. However, in symptomatic ECAS, the LT group demonstrated a higher rate of regression (50.0% vs. 15.0%) and a lower rate of progression (3.8% vs. 10.0%) than the HT group ($P=0.044$) (Table 2). Interaction analysis showed a non-significant ($P=0.080$), yet distinct trend for favorable vascular changes in the LT group in the symptomatic ECAS compared with the symptomatic ICAS (Figure 1).

Although our study provided longitudinal data on MRA findings, the inclusion of only 31% of the original patient cohort

Table 1. Baseline characteristics

	Lower target group (n=120)	Higher target group (n=100)	*P*
Age (yr)	62±10	61±11	0.499
Male sex	85 (70.8)	68 (68.0)	0.649
Body mass index (kg/m^2)	25±4	24±3	0.065
Entry event			0.155
Ischemic stroke	114 (95.0)	90 (90.0)	
TIA	6 (5.0)	10 (10.0)	
Time since entry event (day)	9 [5–20]	7 [4–18]	0.542
Previous mRS score	1 [0–2]	1 [0–2]	0.728
Medical history			
Hypertension	62 (51.7)	62 (62.0)	0.124
Diabetes mellitus	43 (35.8)	32 (32.0)	0.521
Hyperlipidemia	68 (56.7)	63 (63.0)	0.379
Smoking history			0.792
Never smoker	59 (49.2)	52 (52.0)	
Former smoker	26 (21.7)	18 (18.0)	
Current smoker	35 (29.2)	30 (30.0)	
Coronary artery disease	10 (8.4)	8 (8.0)	0.967
Previous stroke history	8 (6.7)	8 (8.0)	0.655
Statin naïve	53 (44.2)	42 (42.0)	0.706
Lab findings			
LDL-C (mg/dL)	131±38	139±40	
HDL-C (mg/dL)	45±12	47±12	
Total cholesterol (mg/dL)	194±46	206±48	
Triglycerides (mg/dL)	152±105	152±96	
Hba1c (%)	6.5±1.4	6.4±1.5	
Location of stenosis			0.715
ICAS	54 (45.0)	45 (45.0)	
ECAS	16 (13.3)	17 (17.0)	
ICAS+ECAS	50 (41.7)	38 (38.0)	
Symptomatic stenosis*			0.735
ICAS	60 (69.8)	52 (72.2)	
ECAS	26 (30.2)	20 (27.8)	
Interval between initial and follow-up imaging (yr)	2 [0–3]	1 [0–3]	0.280

Results presented as mean±standard deviation, number (%), or median [interquartile range].
TIA, transient ischemic attack; mRS, modified Rankin Scale; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis.
*Percentages for symptomatic ICAS and ECAS subcategories were calculated using the number of patients with symptomatic stenosis as the denominator (n=86 for the lower target group; n=72 for the higher target group).

Table 2. Differences in stenosis between the lower and higher target groups

Symptomatic+asymptomatic	Lower target group (n=120)	Higher target group (n=100)	*P*
Stenosis			0.322
No change	47 (39.2)	46 (46.0)	
Regression	54 (45.0)	35 (35.0)	
Progression	19 (15.8)	19 (19.0)	
ECAS*			0.363
No change	6 (37.5)	7 (41.2)	
Regression	8 (50.0)	5 (29.4)	
Progression	2 (12.5)	5 (29.4)	
ICAS*			0.322
No change	23 (42.6)	26 (57.8)	
Regression	21 (38.9)	13 (28.9)	
Progression	10 (18.5)	6 (13.3)	
ECAS+ICAS*			0.679
No change	18 (36.0)	13 (34.2)	
Regression	25 (50.0)	17 (44.7)	
Progression	7 (14.0)	8 (21.1)	
Symptomatic	**Lower target group (n=86)**	**Higher target group (n=72)**	***P***
Symptomatic stenosis			0.207
No change	43 (50.0)	44 (61.1)	
Regression	38 (44.2)	22 (30.6)	
Progression	5 (5.8)	6 (8.3)	
Symptomatic ECAS†			0.044
No change	12 (46.2)	15 (75.0)	
Regression	13 (50.0)	3 (15.0)	
Progression	1 (3.8)	2 (10.0)	
Symptomatic ICAS†			0.854
No change	31 (51.7)	29 (55.8)	
Regression	25 (41.7)	19 (36.5)	
Progression	4 (6.7)	4 (7.7)	

Results presented as number (%).
ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis.
*Percentages for each subcategory (ECAS, ICAS, and ECAS+ICAS) were calculated using the total number of patients in each specific subgroup as the denominator, rather than the entire study population (n=120 or n=100); †Percentages for each symptomatic subcategory (ECAS and ICAS) were calculated using the number of patients in each respective symptomatic subgroup as the denominator.

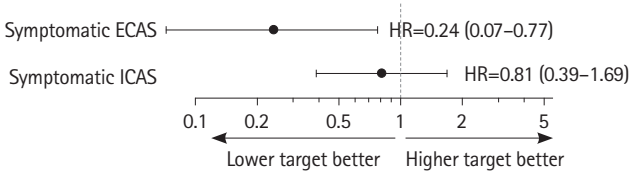

Figure 1. Interaction analysis according to the location of symptomatic cerebral atherosclerosis. HR, hazard ratio; ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis.

warrants careful interpretation. This subset was not randomized, and the decision to perform follow-up imaging was made at the discretion of the clinicians. The higher prevalence of symptomatic stenosis and vascular risk factors in the analyzed group suggests a severity bias. Clinicians are likely to prioritize follow-ups for patients presumed to be at a higher risk of disease progression or recurrent events. Consequently, our findings may have overestimated the rate of vascular changes compared with those of asymptomatic or lower-risk patients.

Nevertheless, our results align with those of a previous study that demonstrated that statins slow the progression of carotid atherosclerosis.[5] The Treat Stroke to Target–Plaque Ultrasound Study also showed that the LT group experienced significantly greater regression of carotid atherosclerosis than the HT group.[6] However, these two studies did not compare the efficacy of the LT strategy between ECAS and ICAS groups. Therefore, our results are unique in showing the different impacts of the LDL-C target according to the location of cerebral atherosclerosis; the LT target is superior to HT in patients with symptomatic ECAS, but not in patients with ICAS. This supports the original Korean TST trial, in which the LT strategy was more effective in preventing recurrent stroke in patients with symptomatic ECAS than in those with ICAS.[2]

Our results may be explained by the differences in anatomical characteristics between the intracranial and extracranial arteries.[7] Compared with extracranial arteries, intracranial arteries have a thinner tunica media, lack vasa vasorum,[7] and possess a more prominent internal elastic lamina. Furthermore, they have a unique embryological origin from the neural crest, whereas extracranial arteries are primarily derived from the mesoderm.[8] The role of hyperlipidemia is significantly greater in patients with symptomatic ECAS than in those with ICAS.[7] In general, ICAS shows features such as fibrosis, small lipid pools, a low grade of inflammation, and relatively low numbers of complicated plaques compared with ECAS.[9] These differences may explain the varied responses to lipid-lowering therapy among different cerebral arteries in our study.

Several studies have shown favorable outcomes with intensive statin therapy in patients with ICAS.[10] The Intensive Statin Treatment in Acute Ischemic Stroke Patients with Intracranial Atherosclerosis-High-Resolution Magnetic Resonance Imaging trial demonstrated plaque stabilization with high-dose statins,[10] and a prespecified analysis of the Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis trial showed the importance of an LDL-C target <70 mg/dL for reducing vascular events in patients with ICAS who were medically treated.[11] However, these are non-controlled studies, and a direct comparison between LT and HT strategies has not been made in patients with ICAS.

Our study had limitations, as only patients who underwent follow-up MRI were included in the analysis, which may have

https://doi.org/10.5853/jos.2025.05652

introduced selection bias. Additionally, the study relied on MRA rather than high-resolution vessel wall imaging, limiting the detailed assessment of plaque changes. Furthermore, although intrinsic hypoplasia of the ACA or VA was classified as no stenosis in this study, given the considerable anatomic variants, the possibility of misclassification between congenital hypoplasia and mild atherosclerotic narrowing cannot be completely excluded. Despite these limitations, in patients with symptomatic ECAS, LT was associated with greater atherosclerotic regression and less progression than HT; however, this was not observed in patients with ICAS. This may explain why a more aggressive LDL-C reduction is needed in patients with ECAS than in those with ICAS.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2025.05652.

Funding statement

This study was funded by Pfizer Inc. in 2020. Pfizer Upjohn merged with Mylan to form Viatris. There was no industry involvement in the conduct, data gathering, or analysis of the trials.

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: Sang Hee Ha, Jong S. Kim. Study design: Sang Hee Ha, Jong S. Kim. Methodology: Sang Hee Ha, Jae-Chan Ryu, Sung Hee Ahn. Data collection: Jae-Chan Ryu, Jae-Kwan Cha, Sang Min Sung, Kyung Bok Lee, Eung-Gyu Kim, Yong-Won Kim, Ji Hoe Heo, Man Seok Park, Kyusik Kang, Byung-Chul Lee, Keun-Sik Hong, Oh Young Bang, Jei Kim. Investigation: Sang Hee Ha, Jae-Chan Ryu, Sung Hee Ahn. Statistical analysis: Sang Hee Ha, Sung Hee Ahn. Writing—original draft: Sang Hee Ha. Writing—review & editing: Sang Hee Ha, Sung Hee Ahn, Jae-Kwan, Jong S. Kim. Funding acquisition: Jong S. Kim. Approval of final manuscript: all authors.

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Received: November 10, 2025
Revised: February 15, 2026
Accepted: April 9, 2026

Supplementary Table 1. Comparison of demographic, clinical, and angiographic characteristics between patients who underwent MRA and those who did not

	Follow-up group (n=220)	Non-follow up group (n=492)	*P*
Age (yr)	61±10	65±11	0.077
Male sex	153 (69.5)	313 (63.6)	0.124
Body mass index (kg/m^2)	25±4	24±3	0.849
Entry event			0.200
Ischemic stroke	204 (92.7)	468 (95.1)	
TIA	16 (7.3)	24 (4.9)	
Time since entry event (day)	9 [4–19]	8 [4–19]	0.311
Previous mRS score	1 [0–2]	1 [1–2]	0.117
Medical history			
Hypertension	124 (56.4)	326 (66.2)	0.004
Diabetes mellitus	75 (34.2)	181 (36.7)	0.410
Hyperlipidemia	131 (59.8)	288 (58.5)	0.988
Smoking history			0.984
Never smoker	111 (50.5)	240 (48.7)	
Former smoker	44 (20.0)	95 (19.3)	
Current smoker	65 (29.5)	145 (29.4)	
Coronary artery disease	18 (8.3)	53 (10.7)	0.271
Previous stroke history	16 (7.4)	69 (14.0)	0.010
Statin naïve	95 (43.4)	212 (43.0)	0.863
LDL targets			0.116
Lower target	120 (54.5)	237 (48.2)	
Higher target	100 (45.5)	255 (51.8)	
Location of stenosis			0.201
ICAS	99 (45.0)	221 (44.9)	
ECAS	33 (15.0)	99 (20.1)	
ICAS+ECAS	88 (40.0)	172 (35.0)	
Symptomatic stenosis	158 (71.8)	307 (62.4)	0.015

Results presented as mean±standard deviation, number (%), or median [interquartile range].
ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis; MRA, magnetic resonance angiography; TIA, transient ischemic attack; mRS, modified Rankin Scale; LDL, low-density lipoprotein.