

Switch to Rosuvastatin Plus Ezetimibe From Statin Monotherapy to Achieve Target LDL-Cholesterol Goal: A Multi-Center, Open-Label, Single-Arm Trial

Hong-Kyun Park,¹ Jong-Ho Park,² Hee-Kwon Park,³ Kyusik Kang,⁴ Keun-Hwa Jung,⁵ Beom Joon Kim,⁶ Jin-Man Jung,⁷ Young Seo Kim,⁸ Yong-Seok Lee,⁹ Hyo Suk Nam,¹⁰ Yeonju Yu,¹¹ Juneyoung Lee,¹¹ Keun-Sik Hong¹

¹Department of Neurology, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea

²Department of Neurology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea

³Department of Neurology, Inha University Hospital, Inha University School of Medicine, Incheon, Korea

⁴Department of Neurology, Nowon Eulji Medical Center, Eulji University School of Medicine, Seoul, Korea

⁵Department of Neurology, Seoul National University Hospital, Seoul, Korea

⁶Department of Neurology, Seoul National University Bundang Hospital, Seongnam, Korea

⁷Department of Neurology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea

⁸Department of Neurology, Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul, Korea

⁹Department of Neurology, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

¹⁰Department of Neurology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

¹¹Department of Biostatistics, Korea University College of Medicine, Seoul, Korea

Dear Sir:

For patients with cerebrovascular disease of atherosclerotic origin, the target low-density lipoprotein cholesterol (LDL-C) level is less than 70 mg/dL.¹ However, despite being on statin monotherapy, approximately 50% of patients fail to achieve the target LDL-C goal.^{2,3} Further LDL-C reduction by increasing statin dosage is limited; doubling the statin dose generally results in only a 5% to 7% absolute reduction. Recent clinical trials involving patients with atherosclerotic cardiovascular disease or recent stroke demonstrated the superiority of the rosuvastatin/ezetimibe combination therapy over doubling rosuvastatin dose for LDL-C reduction.^{4,5} However, there is no salient data on achieving target LDL-C goals by adding ezetimibe in Korean patients with ischemic stroke, transient ischemic attack (TIA), or cerebral atherosclerosis who were indicated for and have been on statin monotherapy. Switch to ROSuvastatin plus Ezetimibe Treatment from statin monotherapy for Target LDL-C goal Achievement in patients with ischemic STROKE, TIA, or cerebral atherosclerosis (S-ROSETTA-Stroke) aimed to evaluate the effectiveness of switch-

ing to combination of ezetimibe and rosuvastatin with equivalent prior statin intensity on achieving LDL-C <70 mg/dL in patients with ischemic stroke, TIA, or cerebrovascular atherosclerosis whose LDL-C was $\geq$ 70 mg/dL despite statin monotherapy.

This was an investigator-initiated, multicenter, open-label, single-arm trial conducted in 10 centers in South Korea. The trial was supported by Samjin Pharm, which provided study medications but had no role in the trial's design, conduct, data collection, analysis, interpretation of data, or preparation of the manuscript. All data were collected by site investigators and monitored by an independent research organization contracted by the principal investigator's academic institution. The trial was registered at cris.nih.go.kr (KCT0008455).

Key inclusion criteria were (1) ischemic stroke, TIA, or cerebral atherosclerosis without clinical cerebral ischemia, (2) statin monotherapy before enrollment, and (3) baseline LDL-C level >70 mg/dL. Detailed inclusion and exclusion criteria are described in the Supplementary Table 1. The local institutional review boards of all participating centers approved the study. Enrolled patients or their legally authorized representatives provided written in-

formed consent.

Following screening, baseline LDL-C and patient characteristics were recorded, and study medication was selected based on the equivalent dose of prior statin intensity (Supplementary Table 2). During the study period, we assessed adherence and adverse events. Final LDL-C levels were measured at day 90±30.

The primary endpoint was the proportion of patients achieving an LDL-C level <70 mg/dL at 90 days. Secondary endpoints included relative and absolute LDL-C reduction, LDL-C level <55 mg/dL, multiple lipid goals achievement (total cholesterol <200 mg/dL, LDL-C <70 mg/dL, and triglyceride <150 mg/dL), major cardiovascular events (including stroke, acute coronary syndrome, revascularization, or vascular death), all cause of death, and new-onset diabetes.

The sample size was calculated by assuming the primary endpoint rate of 60% with a 95% confidence interval (CI) of 55%–65% at a significance level of 0.05, based on the findings of ROSETTA-Stroke, which enrolled statin-naïve Korean patients with acute ischemic stroke.⁵ Accounting for a 10% dropout rate, the planned sample size was 410. Efficacy endpoints were analyzed using the modified intention-to-treat (mITT) population, which included patients who took at least one dose of the study medications and completed LDL-C measurements at 90 days. Per-protocol analysis included patients who had no major protocol violation, took more than 80% of the study medications, and did not take non-study lipid-lowering agents. The safety population comprised patients who were enrolled and took at least one dose of study medication.

Between July 23, 2023, and August 24, 2024, 410 patients were enrolled; 397 patients were included in the safety population, 381 in the mITT population, and 340 in the per-protocol (PP) population (Supplementary Figure 1). Table 1 presents detailed baseline characteristics. The mean age was 66.4 years, and 35.4% were female. Prior to enrollment, atorvastatin (60%) and rosuvastatin (30%) were the predominant statins used, with varying intensities: low (40%), moderate (37%), and high (23%). The mean baseline LDL-C level was 94.5 mg/dL.

The study met the primary endpoint, with 74.3% of patients achieving LDL-C levels <70 mg/dL at 90 days. Secondary outcomes showed a 33.1% relative LDL-C reduction, a 32.3 mg/dL absolute LDL-C reduction, with 41.2% of patients reaching <55 mg/dL and 63% meeting multiple lipid goals. One major vascular event occurred (recurrent ischemic stroke), with no deaths or new diabetes cases reported (Table 2). The results of the PP population analyses were consistent with those of the mITT population analyses (Supplementary Tables 3 and 4). In subgroup analyses, males, patients aged ≥70 years, those with prior moderate or high-intensity statin use, and those with baseline LDL-C

<100 mg/dL were more likely to achieve the target LDL-C goal (Supplementary Figure 2).

In terms of safety, 13.4% of patients experienced any adverse events, and 2% had treatment-emergent adverse events (TEAEs). There were no cases of rhabdomyolysis, and only 0.8% had significant liver enzyme elevation. There was 1 case of serious TEAE of acute pancreatitis, which was resolved after stopping the study

Table 1. Baseline characteristics of the study population (mITT population)

Characteristics	Value (n=381)
Age (yr)	66.4±10.8
Female sex	135 (35.4)
Qualifying event	
Ischemic stroke	279 (73.2)
Large artery atherosclerosis	85 (30.5)
Small vessel occlusion	106 (38.0)
Cardioembolism	20 (7.2)
Other determined	10 (3.6)
Undetermined	58 (20.8)
TIA	33 (8.7)
Cerebral atherosclerosis w/o clinical stroke/TIA	69 (18.1)
Prior statins	
Atorvastatin	230 (60.4)
Rosuvastatin	113 (29.7)
Pitavastatin	38 (10.0)
Prior statin intensity	
Low	150 (39.8)
Moderate	141 (37.4)
High	86 (22.8)
Body mass index (kg/m ²)	25.0±3.5
Blood pressure (mm Hg)	
Systolic blood pressure	130.5±15.7
Diastolic blood pressure	75.0±12.7
Vascular risk factors	
Hypertension	294 (77.2)
Dyslipidemia	365 (95.8)
Diabetes	111 (29.1)
Current smoking	67 (17.6)
Coronary heart disease	27 (7.1)
Lipid profiles (mg/dL)	
Low-density lipoprotein cholesterol	94.5±19.8
Total cholesterol	162.9±24.6
Triglyceride	128.6±60.1
High-density lipoprotein cholesterol	52.1±12.0
Glucose (mg/dL)	114.5±35.5
Glycated hemoglobin	6.1±0.8

Values are presented as mean±standard deviation or n (%).

mITT, modified intention-to-treat; TIA, transient ischemic attack.

medication (Table 3).

This trial showed that switching to ezetimibe plus rosuvastatin of equivalent intensity to prior statins resulted in a substantial LDL-C reduction. Three-quarters of patients achieved the target LDL-C goal of <70 mg/dL. In addition, 41.2% had LDL-C <55 mg/dL, the relative LDL-C reduction was 33.1%, and the absolute LDL-C reduction was 32.3 mg/dL, along with 63% of multiple lipid goal achievement rate. Given the 2% of TEAE and only one reversible serious TEAE, the safety of this switching strategy looks acceptable.

Our findings align with previous studies on the efficacy of combining ezetimibe with statins for LDL-C reduction. In a prior meta-analysis, the relative reduction with adding ezetimibe to ongoing statins was 26.0%.⁶ The relative LDL-C reduction of 33.1% observed in this trial looks greater. For clinical efficacy with LDL-C reduction, prior meta-analyses indicated that 39 mg/dL decrease in the achieved LDL-C level was associated with a stroke risk reduction of 21.1%–23.5%.^{7,8} When applying the result of S-ROSETTA-Stroke trial to the existing data, the absolute LDL-C reduction of 32.3 mg/dL in this trial would be expected to result in around 20% reduction in future stroke risk by adding ezetimibe.

Table 2. Study outcomes (mITT population, n=381)

Study outcomes	n	Value
Primary endpoint		
LDL-C reduction <70 mg/dL (%)	283	74.3 (69.6–78.6)
Secondary endpoints		
Relative LDL-C reduction (%)		33.1±22.8
Absolute LDL-C reduction (mg/dL)		32.3±25.0
LDL-C reduction <55 mg/dL (%)	157	41.2 (36.2–46.3)
Multiple lipid goal achievement (%)*	240	63.0 (57.9–67.9)
Major vascular events	1	0.26 (0.01–1.45)
Recurrent stroke	1	0.26 (0.01–1.45)
All-cause death	0	–
New onset diabetes	0	–

Values are presented as rate (95% CI) or mean±standard deviation. mITT, modified intention-to-treat; CI, confidence interval; SD, standard deviation; LDL-C, low-density lipoprotein cholesterol. *Total cholesterol <200 mg/dL, LDL-C <70 mg/dL, and triglyceride <150 mg/dL at follow-up visit.

Table 3. Adverse events (safety population)

Adverse event	Value (n=397)
Any adverse event	53 (13.4)
TEAE	8 (2.0)
Any serious adverse event	6 (1.5)
Serious TEAE	1 (0.3)

Values are presented as n (%). TEAE, treatment-emergent adverse event.

This study has several limitations as follows. The primary endpoint was the LDL-C level rather than clinical outcomes. The short follow-up period restricts the ability to assess long-term efficacy and safety, potentially underestimating treatment effects or failing to detect delayed adverse events. The open-label design may be liable to reporting bias for clinical endpoints. Finally, the exclusive enrollment of Korean patients limits the generalizability of the results to other populations.

In conclusion, switching to ezetimibe plus rosuvastatin with equivalent prior statin intensity resulted in a substantial LDL-C lowering reduction with favorable safety profiles in Korean patients with ischemic stroke, TIA, or cerebral atherosclerosis who are indicated for lipid-lowering therapy, suggesting this approach as an effective strategy for achieving the target LDL-C level when LDL-C lowering with statin monotherapy is insufficient.

Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2024.05015>.

Funding statement

This study was funded by Samjin Pharm.

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: KSH, HKP (Hong-Kyun Park). Study design: KSH, HKP (Hong-Kyun Park), JL. Methodology: KSH, HKP (Hong-Kyun Park), JL. Data collection: KSH, HKP (Hong-Kyun Park), JHP, HKP (Hee-Kwon Park), KK, KHJ, BJK, MJM, YSK, YSL, HSN. Investigation: KSH, HKP (Hong-Kyun Park), JHP, HKP (Hee-Kwon Park), KK, KHJ, BJK, MJM, YSK, YSL, HSN. Statistical analysis: KSH, YY, JL. Writing—original draft: KSH, HKP (Hong-Kyun Park). Writing—review & editing: all authors. Funding acquisition: KSH. Approval of final manuscript: all authors.

References

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(5):e526–e677.

- cal Practice Guidelines. *Circulation* 2019;139:e1082–e1143.
2. Gitt AK, Drexel H, Feely J, Ferrières J, Gonzalez-Juanatey JR, Thomsen KK, et al. Persistent lipid abnormalities in statin-treated patients and predictors of LDL-cholesterol goal achievement in clinical practice in Europe and Canada. *Eur J Prev Cardiol* 2012;19:221–230.
 3. Park JE, Chiang CE, Munawar M, Pham GK, Sukonthasarn A, Aquino AR, et al. Lipid-lowering treatment in hypercholesterolaemic patients: the CEPHEUS Pan-Asian survey. *Eur J Prev Cardiol* 2012;19:781–794.
 4. Kim BK, Hong SJ, Lee YJ, Hong SJ, Yun KH, Hong BK, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. *Lancet* 2022;400:380–390.
 5. Hong KS, Bang OY, Park JH, Jung JM, Lee SH, Song TJ, et al. Moderate-intensity rosuvastatin plus ezetimibe versus high-intensity rosuvastatin for target low-density lipoprotein cholesterol goal achievement in patients with recent ischemic stroke: a randomized controlled trial. *J Stroke* 2023;25:242–250.
 6. Ambegaonkar BM, Tipping D, Polis AB, Tomassini JE, Tershakovec AM. Achieving goal lipid levels with ezetimibe plus statin add-on or switch therapy compared with doubling the statin dose. A pooled analysis. *Atherosclerosis* 2014;237:829–837.
 7. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol* 2009;8:453–463.
 8. Shin J, Chung JW, Jang HS, Lee J, Hong KS, Bang OY, et al. Achieved low-density lipoprotein cholesterol level and stroke risk: a meta-analysis of 23 randomised trials. *Eur J Prev Cardiol* 2021;28:905–916.
-
- Correspondence:** Keun-Sik Hong
Department of Neurology, Inje University Ilsan Paik Hospital, 170 Juhwa-ro, Ilsanseo-gu, Goyang 10380, Korea
Tel: +82-31-910-7680
E-mail: nrhks455@gmail.com
<https://orcid.org/0000-0002-4684-6111>
- Received: November 20, 2024
Revised: December 24, 2024
Accepted: February 25, 2025
-

Supplementary Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Ischemic stroke, TIA, or cerebral atherosclerosis without clinical cerebral ischemia
2. On statin monotherapy
3. Baseline LDL-C level >70 mg/dL
4. Age 19 or more
5. Written informed consent
Exclusion criteria
1. Planned vascular intervention during the study period
2. Significant hepatic impairment (ALT or AST >120 IU/L)
3. Allergy or contraindication to rosuvastatin or ezetimibe
4. Alcohol or drug addiction
5. Pregnancy or breast-feeding
6. Women unwilling to continue contraception during the study period
7. Severe anemia: Hb level <10 g/dL for men and <9 g/dL for women
8. Malignancy or other serious medical conditions with a life expectancy <6 months
9. Treatment with cyclosporine or protease
10. Renal impairment with creatinine clearance <30 mL/min
11. Inability or unwillingness to comply with study-related procedures
12. Participation in other clinical trials within 3 months
13. Employees of the investigator or study center, with direct involvement in the current study
14. Other reasons deemed inappropriate for participation in the trial, judged by investigators
TIA, transient ischemic attack; LDL-C, low-density lipoprotein cholesterol; ALT, alanine transaminase; AST, aspartate transaminase.

Supplementary Table 2. Study medications according to the prior statin type and dose

Prior statin type	Prior statin dose (mg)	Study medications
Rosuvastatin	5	Ezetimibe/Rosuvastatin 10/5 mg
	10	Ezetimibe/Rosuvastatin 10/10 mg
	20	Ezetimibe/Rosuvastatin 10/20 mg
Atorvastatin	10	Ezetimibe/Rosuvastatin 10/5 mg
	20	Ezetimibe/Rosuvastatin 10/10 mg
	40	Ezetimibe/Rosuvastatin 10/20 mg
Simvastatin	20	Ezetimibe/Rosuvastatin 10/5 mg
	40	Ezetimibe/Rosuvastatin 10/10 mg
Pitavastatin	2	Ezetimibe/Rosuvastatin 10/5 mg
	4	Ezetimibe/Rosuvastatin 10/10 mg

Supplementary Table 3. Baseline characteristics of the study population (per-protocol population)

Characteristics	Value (n=340)
Age (yr)	66.2±10.5
Female sex	117 (34.3)
Qualifying event	
Ischemic stroke	253 (74.4)
Large artery atherosclerosis	79 (31.2)
Small vessel occlusion	97 (38.3)
Cardioembolism	18 (7.1)
Other determined	9 (3.6)
Undetermined	50 (19.8)
TIA	29 (8.5)
Cerebral atherosclerosis w/o clinical stroke/TIA	58 (17.1)
Prior statins	
Atorvastatin	206 (60.6)
Rosuvastatin	98 (28.8)
Pitavastatin	36 (10.6)
Prior statin intensity	
Low	133 (39.1)
Moderate	126 (37.1)
High	91 (23.8)
Body mass index (kg/m ²)	24.9±3.5
Blood pressure (mm Hg)	
Systolic blood pressure	130.1±15.6
Diastolic blood pressure	74.7±12.4
Vascular risk factors	
Hypertension	263 (77.4)
Dyslipidemia	325 (95.6)
Diabetes	95 (27.9)
Current smoking	56 (16.5)
Coronary heart disease	26 (7.7)
Lipid profiles (mg/dL)	
Low-density lipoprotein cholesterol	94.7±19.5
Total cholesterol	163.3±24.7
Triglyceride	128.2±60.4
High-density lipoprotein cholesterol	52.2±12.1
Glucose (mg/dL)	114.4±36.5
Glycated hemoglobin (%)	6.1±0.8

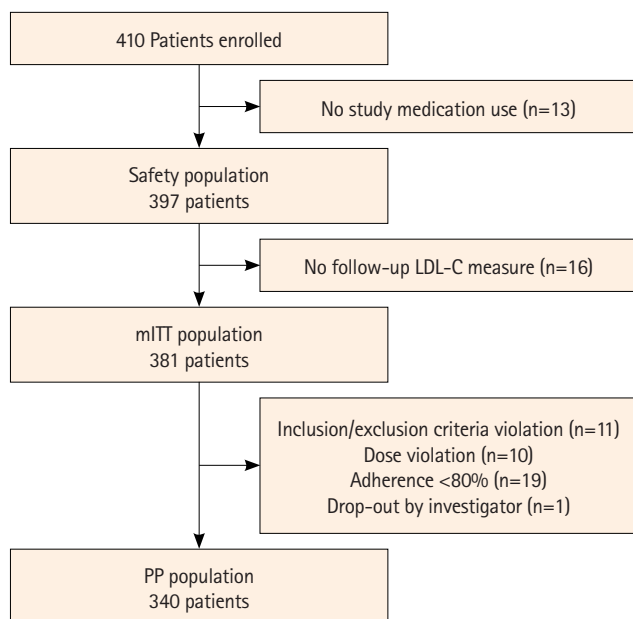
Values are presented as mean±standard deviation or n (%).
TIA, transient ischemic attack.

Supplementary Table 4. Study outcomes (per-protocol population, n=340)

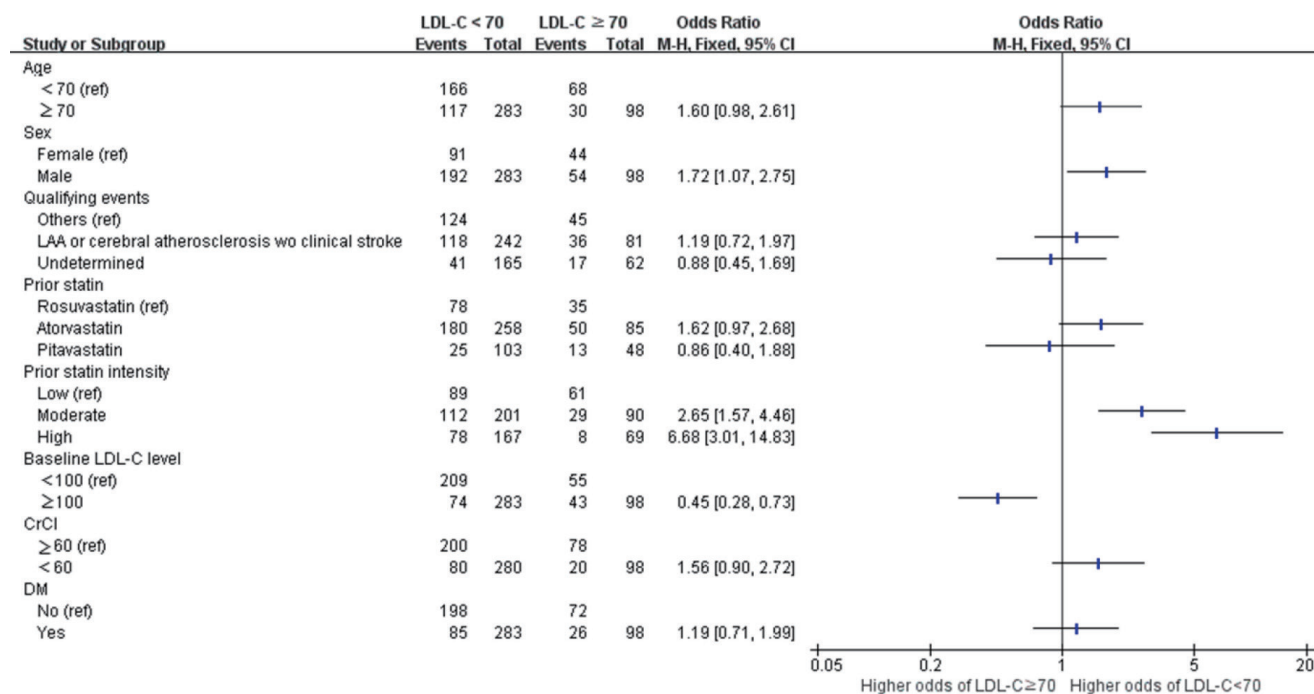
Study outcomes	n	Value
Primary endpoint		
LDL-C reduction <70 mg/dL (%)	256	75.3 (70.4–79.8)
Secondary endpoints		
Relative LDL-C reduction (%)		34.8±19.1
Absolute LDL-C reduction (mg/dL)		33.8±21.9
LDL-C reduction <55 mg/dL (%)	144	42.4 (37.0–47.8)
Multiple lipid goal achievement (%)*	221	65.0 (59.7–70.1)
Major vascular events	1	0.29 (0.01–1.63)
Recurrent stroke	1	0.29 (0.01–1.63)
All-cause death	0	–
New onset diabetes	0	–

Values are presented as rate (95% CI) or mean±standard deviation.
mITT, modified intention-to-treat; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol.

*Total cholesterol <200 mg/dL, LDL-C <70 mg/dL, and triglyceride <150 mg/dL at follow-up visit.



Supplementary Figure 1. Study enrollment flow and populations analyzed. LDL-C, low-density lipoprotein cholesterol; mITT, modified intention-to-treat; PP, per-protocol.



Supplementary Figure 2. Subgroup analysis (mITT population). mITT, modified intention-to-treat; LDL-C, low-density lipoprotein cholesterol; M-H, Mantel-Haenszel; CI, confidence interval; LAA, large artery atherosclerosis; CrCl, creatinine clearance; DM, diabetes mellitus.