Journal of the American Heart Association

Check for updates

PROTOCOL

SVO70 (Optimal Target Low-Density Lipoprotein Cholesterol Level for Small Vessel Occlusion Stroke): Rationale and Study Design

Wookjin Yang, MD, PhD*; Tae-Jin Song, MD, PhD*; Seong-Ho Koh, MD, PhD; Hye Seon Jeong, MD, PhD; Sung-Il Sohn, MD, PhD; Young Seo Kim, MD, PhD; Beom Joon Kim, MD, PhD; Jin-Man Jung, MD, PhD; Keun-Hwa Jung, MD, PhD; Jeong-Min Kim, MD, PhD; Hyemin Jang, MD, PhD; Eung-Joon Lee, MD; Matthew Chung, MD; Seongheon Kim, MD; Hee-Kwon Park, MD, PhD; Sungwook Yu, MD, PhD; Yong-Jin Cho, MD, PhD; Joon-Tae Kim, MD, PhD; Yerim Kim, MD, PhD; Chulho Kim, MD, PhD; Hahn Young Kim, MD, PhD; Mi Sun Oh, MD, PhD; Do-Hyung Kim, MD, PhD; Yeong-Bae Lee, MD, PhD; Mi-Yeon Eun, MD; Hyun Young Park, MD, PhD; Kyusik Kang, MD, PhD; Hyung-Min Kwon, MD, PhD; Han-Jin Cho, MD, PhD; Jae Guk Kim, MD, PhD; Jay Chol Choi, MD, PhD; Joonsang Yoo, MD, PhD; Hyo Suk Nam, MD, PhD; Taedong Ok, MD, PhD; A-Hyun Cho, MD, PhD; Jong Yun Lee, MD, PhD; Je-Young Shin, MD; Joong Hyun Park, MD; Kwang-Yeol Park, MD, PhD; Dong-Ick Shin, MD, PhD; Youngrok Do, MD, PhD; Yoonkyung Chang, MD, PhD; SunHye Jung, MD; Yo Han Jung, MD, PhD; Woo-Keun Seo, MD, PhD; Sang-Wuk Jeong, MD, PhD; Sam Yeol Ha, MD, PhD; Sang Joon An, MD; Seong Hwan Ahn, MD, PhD; Yang-Ha Hwang, MD, PhD; Seung-Hoon Lee, MD, PhD

BACKGROUND: Current stroke guidelines lack subtype-specific recommendations for optimal low-density lipoprotein cholesterol targets. Indeed, most lipid-lowering trials have not differentiated between stroke subtypes or focused primarily on large artery atherosclerosis, leaving a gap in evidence for other stroke subtypes, such as small vessel occlusion stroke. This study is designed to evaluate whether intensive lipid-lowering therapy is superior to standard therapy in reducing major adverse cardiovascular events among patients with small vessel occlusion stroke.

METHODS: SVO70 (Optimal Target Low-Density Lipoprotein Cholesterol Level for Small Vessel Occlusion Stroke) is a multicenter, prospective, randomized, open, blinded-end point clinical trial in which adult patients with neuroimaging-confirmed small vessel occlusion stroke within 180 days of randomization will be enrolled. Key exclusion criteria include predefined low-density lipoprotein cholesterol targets for other comorbidities, contraindications to statin, and pregnancy or lactation. Eligible participants will be randomized 1:1 to achieve low-density lipoprotein cholesterol <70 mg/dL (intensive group) or 90 to 110 mg/dL (standard group). The trial aims to enroll 4016 participants over a 2-year recruitment period, with a minimum follow-up of 4 years. The primary end point is the occurrence of major adverse cardiovascular events, defined as cardiovascular death, stroke, and acute coronary syndrome, during the follow-up period. Secondary end points include (1) any stroke, (2) ischemic stroke or transient ischemic attack, (3) hemorrhagic stroke, (4) cardiovascular death, (5) myocardial infarction, (6) all-cause death, and (7) acute coronary syndrome.

CONCLUSIONS: This study will provide valuable information for determining optimal low-density lipoprotein cholesterol targets for patients with small vessel occlusion stroke.

Correspondence to: Seung-Hoon Lee, MD, PhD, FAHA, Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea. Email: sb0516@snu.ac.kr

*W. Yang and T.-J. Song contributed equally.

This article was sent to Fadar O. Otite, MD, SM, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.046824

For Sources of Funding and Disclosures, see page 7.

© 2026 The Author(s). Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

Downloaded from http://ahajournals.org by on September 30, 2026

REGISTRATION: URL: https://ClinicalTrials.gov; Unique Identifier: NCT06649240, Clinical Research Information Service (KCT0009043).

Key Words: cerebral small vessel disease ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ ischemic stroke ■ LDL cholesterol ■ secondary prevention

CLINICAL PERSPECTIVE

What Is New?

- SVO70 (Optimal Target Low-Density Lipoprotein Cholesterol Level for Small Vessel Occlusion Stroke) is the first randomized clinical trial evaluating optimal low-density lipoprotein cholesterol targets specifically in patients with small vessel occlusion stroke.

What Are the Clinical Implications?

- The findings of this trial may help inform future subtype-specific strategies for lipid management and stroke prevention in patients with small vessel occlusion stroke.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiovascular events
SVO	small vessel occlusion

Lipid-lowering therapy plays a central role in reducing cardiovascular risk, with strong evidence supporting that lower low-density lipoprotein cholesterol (LDL-C) levels improve clinical outcomes.[1–6] Nevertheless, clinical guidelines for stroke prevention still exhibit notable gaps. Current guidelines recommend an LDL-C target of <70 mg/dL for patients with ischemic stroke attributable to large artery atherosclerosis,[7] based on findings from the TST (Treat Stroke to Target) trial.[8] However, other ischemic stroke subtypes remain unaddressed, reflecting the lack of evidence-based recommendations beyond atherosclerotic stroke. Among these subtypes, small vessel occlusion (SVO) is particularly noteworthy, accounting for approximately one quarter of all ischemic strokes and exhibiting higher prevalence among Asian populations.[7,9] Although hypertension is the primary risk factor for SVO stroke, evidence indicates that dyslipidemia may also contribute to its pathogenesis. Microatheroma at perforator origins—which commonly presents as branch atheromatous disease—is a key pathophysiologic mechanism of SVO, and may plausibly respond to antiatherogenic lipid-lowering therapy.[10–12] Prior studies using Mendelian randomization analyses have suggested that genetically proxied lowering of LDL-C is associated with a reduced risk of the SVO subtype.[13,14]

The absence of SVO-specific guidance reflects a broader limitation in the current evidence base. Most lipid-lowering trials involving patients with ischemic stroke have either not stratified participants by stroke subtype or have focused primarily on atherosclerotic disease.[3,8,15] Consequently, clinical decision-making for patients with SVO stroke has largely depended on post hoc analyses of trials not specifically designed to address pathogenetic heterogeneity. To address this gap, the SVO70 (Optimal Target Low-Density Lipoprotein Cholesterol Level for Small Vessel Occlusion Stroke) trial compares intensive versus standard lipid-lowering strategies in patients with SVO stroke, aiming to inform future guidelines and improve secondary prevention in this population.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Design

The SVO70 trial is a multicenter, prospective, randomized, open-label, blinded end point study designed as a superiority trial to evaluate whether intensive lipid-lowering therapy is more effective than standard therapy in reducing the risk of major adverse cardiovascular events (MACE) in patients with SVO stroke. The overall study design and procedures are illustrated in Figure 1. Participants will be recruited over a 2-year period and followed up for at least 4 years. Initial ethical approval was granted by the institutional review board of Seoul National University Hospital (IRB No. H-2310-119-1479) in November 2023. Approvals from the institutional review boards of all participating sites were subsequently obtained. Written informed consent must be provided by all participants or their legally authorized representatives before enrollment. Enrollment began in October 2024, and as of December 2025, 46 stroke centers across Korea are actively recruiting participants.

Downloaded from http://ahajournals.org by on September 30, 2026

Patient Population

Eligible patients are those with symptomatic ischemic stroke in the subcortical region or brainstem attributable to SVO. The qualifying lesion must be confirmed by neuroimaging, either brain computed tomography or magnetic resonance imaging, as determined by the investigator. As a reference, typical radiological criteria may be applied: lesions ≤20 mm in maximum diameter if assessed within 3 weeks of onset, or ≤15 mm if assessed after 3 weeks, regardless of imaging modality.[16] The index stroke must have occurred within 180 days before enrollment.

Inclusion and Exclusion Criteria

Inclusion Criteria

Participants must satisfy all the following eligibility criteria.

1. Age ≥19 years.
2. Presence of subcortical or brainstem SVO lesions confirmed by neuroimaging.
3. History of symptomatic ischemic stroke attributable to the qualifying SVO lesion within 180 days before enrollment.
4. Provision of written informed consent by the participant or a legally authorized representative.

Exclusion Criteria

Participants who meet any of the following exclusion criteria will be excluded.

1. Comorbidities requiring LDL-C management to a prespecified target (eg, <70 mg/dL) according to contemporary guidelines. The following conditions apply with operational criteria:
   a. Extracranial/intracranial large artery stenosis ≥50%.
   b. History of atherosclerotic ischemic stroke or transient ischemic attack.
   c. Documented coronary artery disease.
   d. Documented peripheral artery disease or aortic atherosclerotic disease.
   e. Diabetes with one or more of the following:
      (i) Duration ≥10 years;
      (ii) ≥2 major risk factors (men ≥45 years, women ≥55 years; family history of premature atherosclerotic cardiovascular diseases; hypertension; current smoking, or high-density lipoprotein cholesterol <40 mg/dL); or
      (iii) Known evidence of target organ damage (albuminuria, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, retinopathy, neuropathy, or left ventricular hypertrophy).[17–19]
2. Baseline LDL-C <70 mg/dL in the absence of lipid-lowering therapy.
3. Known contraindications to statin therapy (active liver disease, serum transaminase levels >3 times the upper limit of normal, clinically significant muscle disorders, hypersensitivity to statins, or concomitant use of contraindicated medications).
4. Pregnant or breastfeeding women or those planning pregnancy during the study period.
5. Any condition deemed by the investigator to preclude sustained participation in a 4-year clinical trial.

Randomization and Treatment

Participants meeting the inclusion/exclusion criteria will be randomized in a 1:1 ratio to either the intensive or standard lipid-lowering therapy group. Randomization

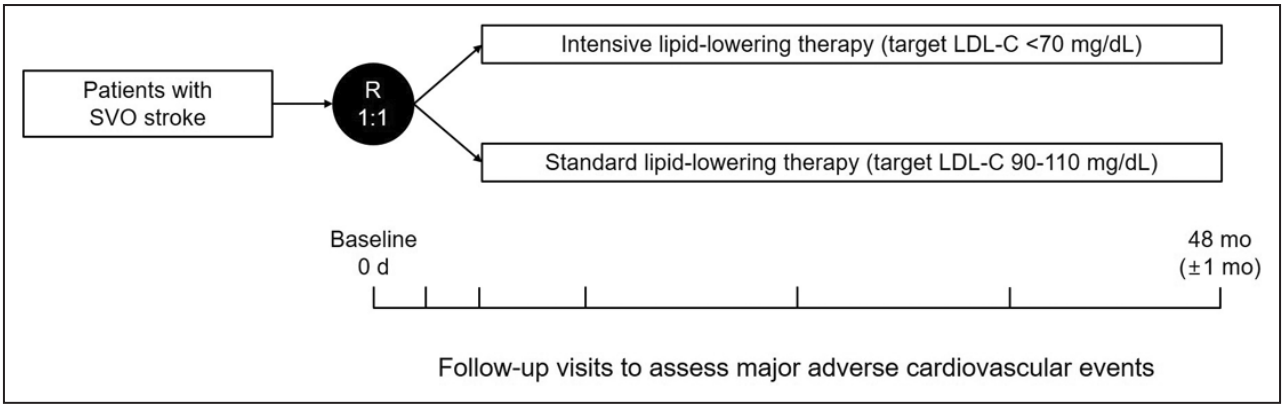


Figure 1. Overview of study design and participant flow.
LDL-C indicates low-density lipoprotein cholesterol; and SVO, small vessel occlusion.

Downloaded from http://ahajournals.org by on September 30, 2026

will be conducted centrally using a secure web-based system (cubeCDMS, https://www.cubecdms.com). To minimize intercenter variability and ensure balanced treatment allocation at each site, a stratified block randomization design will be used, with stratification by participating center and baseline LDL-C (<70 versus ≥70 mg/dL). Randomization numbers will be generated using permuted blocks of size 4 and 6, with the block order randomly varied to minimize predictability. Allocation concealment will be ensured through a centralized interactive web response system, which maintains the site-specific randomization list inaccessible to investigators and discloses the assigned treatment strictly at the point of allocation.

Following allocation, participants will receive lipid-lowering therapy according to the assigned LDL-C target. The intensive lipid-lowering therapy group will target LDL-C <70 mg/dL, and the standard group will target 90 to 110 mg/dL. Lipid control will be guided by the treating investigator, primarily using statins and, when appropriate, ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors. To support decision-making when LDL-C values fall outside the assigned target range, a nonmandatory framework for treatment adjustment is provided as a reference (Figure 2), whereas the choice and modification of therapy will ultimately remain with the treating physician. All other aspects of clinical care will follow established standard-of-care stroke guidelines.

Participants will undergo scheduled assessments at baseline and at 3, 6, 12, 24, 36, and 48 months following randomization. At each visit, key data will be collected, including clinical events, treatment adherence, and concomitant medications. Adherence will be monitored using prescription refill data and patient self-reports. Additionally, LDL-C levels obtained at routine visits may provide supportive insight into treatment compliance. Lipid profiles will be measured to guide lipid-lowering management. Outcome and safety data will be collected throughout the follow-up period, preferably through on-site visits; telephone contact will be used when in-person visits are not feasible to minimize loss to follow-up and ensure a complete outcome assessment (Figure 3).

Primary End Point

The primary end point is the occurrence of MACE, defined as a composite of cardiovascular death, stroke (ischemic or hemorrhagic), and acute coronary syndrome, including ST-segment–elevation myocardial infarction, non–ST-segment–elevation myocardial infarction, and unstable angina requiring hospitalization.

Secondary End Points

Secondary end points include (1) any stroke, (2) ischemic stroke or transient ischemic attack, (3) hemorrhagic stroke, (4) cardiovascular death, (5) myocardial infarction, (6) all-cause death, and (7) acute coronary syndrome.

Data Monitoring Committee

An independent Data Monitoring Committee will safeguard participant welfare and ensure the scientific integrity of the trial. The Data Monitoring Committee will consist of 3 members, including 1 statistician and 2 neurologists who are not otherwise involved in the conduct of the study. The Data Monitoring Committee will periodically review safety data and will also review interim analysis results and may recommend continuation or early termination of the trial for benefit, harm, or futility.

Sample Size Estimates

The required sample size was calculated for a superiority trial comparing intensive versus standard LDL-C targets in patients with SVO stroke, assuming a 2-year recruitment period and ≥4 years of follow-up. A single interim analysis is planned when ~50% of the required primary end point events have occurred. As no prior randomized trial has focused exclusively on the effect of lipid-lowering therapy in this population, event rate assumptions were informed by a post hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial, in which 141 MACE occurred among 701 patients with SVO stroke in the control arm over a median follow-up of 4.9 years (event rate: 20.1%, 4.105 per 100 person-years). A post hoc analysis reported a 16% relative risk reduction in MACE with high-intensity statin therapy (hazard ratio, 0.84 [95% CI, 0.66–1.08]).[20] Assuming a 20% relative risk reduction based on our more stringent LDL-C target, the estimated 4-year cumulative incidence of MACE was 16.420% in the standard group and 13.367% in the intensive group. The 4-year incidence of noncardiovascular death, treated as a competing risk, was estimated at 2.375%, based on national mortality statistics.[21] Under these assumptions, 631 MACE events are required to detect superiority using a 2-sided Gray's test with 80% power and a 5% significance level, corresponding to a total sample size of 3510 participants. To account for an anticipated 10% dropout rate, the sample size was increased to 3900. Incorporating a group sequential design to permit interim monitoring for efficacy and futility, Hwang–Shih–DeCani spending functions (γ=–4 for efficacy, γ=–2 for futility) were applied to control the overall type I error rate. This adjustment increased the required number of events to 649. Accordingly, the final sample size was set at 4016 participants (2008 per group), ensuring adequate statistical power while allowing for interim monitoring.

Downloaded from http://ahajournals.org by on September 30, 2026

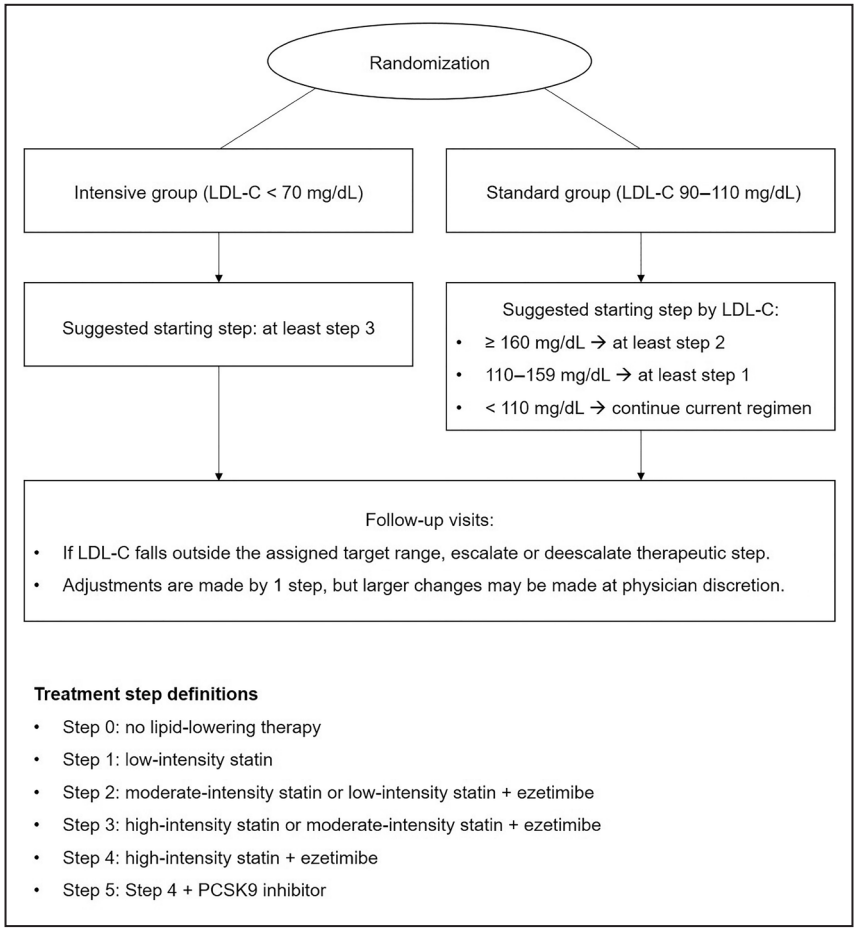


Figure 2. Reference framework to guide lipid-lowering therapy selection and adjustment according to LDL-C targets.
This framework is optional, and lipid-lowering therapy remains individualized at discretion of the physician. LDL-C indicates low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin/kexin type 9.

Prespecified Subgroup Analyses

Prespecified subgroup analyses will evaluate whether the treatment effect varies across clinically relevant patient characteristics, including age, sex, body mass index (<25 versus 25–30 versus >30 kg/m^2), hypertension, diabetes, smoking status, alcohol consumption, baseline LDL-C level (<70 versus ≥70 mg/dL), prior statin therapy, the interval from stroke onset to randomization (≤30 versus >30 days), and infarct location (anterior versus posterior circulation).

Statistical Analysis

Baseline characteristics will be summarized by treatment group. Baseline summaries will be descriptive, and no significance testing will be performed. Continuous variables will be presented as mean±SD or median (interquartile range), and categorical variables as n (%).

The primary efficacy analysis will be conducted in the modified intention-to-treat population, which includes all randomized participants who received at least one dose of the lipid-lowering medication. A per-protocol set will also be analyzed, comprising participants with ≥80% treatment adherence, as assessed by prescription refill records and patient self-reporting, and no major protocol violations. Cumulative incidence functions for MACE will be estimated by treatment group, treating noncardiovascular death as a competing risk. Between-group comparisons will be made using Gray's test. Effect sizes will be reported as subdistribution hazard ratios with 95% CIs, derived from Fine–Gray competing-risks regression models. At the planned interim analysis, scheduled after ~50% of the required MACE events have accrued, prespecified stopping boundaries based on the Hwang–Shih–DeCani spending functions will be applied to assess early efficacy or futility. Secondary time-to-event end

Downloaded from http://ahajournals.org by on September 30, 2026

	STUDY PERIOD							
	Screening	Baseline	Treatment period					Close-out
TIME POINT	-14 d to -1 d	0 d	3 mo (± 14 d)	6 mo (±1 mo)	12 mo (±1 mo)	24 mo (±1 mo)	36 mo (±1 mo)	48 mo (±1 mo)
ENROLLMENT:								
Inclusion/exclusion criteria	■	■						
Informed consent	■							
Randomization		■						
INTERVENTIONS:								
Intensive lipid-lowering group		♦—	—	—	—	—	—	—♦
Standard lipid-lowering group		♦—	—	—	—	—	—	—♦
ASSESSMENTS:								
Demographics/medical history	■							
Index stroke information	■							
Physical assessments	■							■
Baseline laboratory tests	■							
Lipid profile/LDL-C level adjustment	■	■	■	■	■	■	■	■
Safety laboratory test (creatinine kinase)	■		■		■			■
Safety laboratory test (hemoglobin A1c)					■			■
Outcome data collection		■	■	■	■	■	■	■
Treatment adherence			■	■	■	■	■	■
Concomitant medications	■	■	■	■	■	■	■	■

Figure 3. Schedule of study enrollment, interventions, and assessments.
LDL-C indicates low-density lipoprotein cholesterol.

points will be analyzed using competing risk methods or Kaplan–Meier methods, depending on the presence of competing risks, as specified later. For any stroke, ischemic stroke or transient ischemic attack, myocardial infarction, and acute coronary syndrome, cumulative incidence functions will be estimated with all-cause death treated as a competing risk and compared between groups using Gray's test. Cardiovascular death will be analyzed similarly, with noncardiovascular death as the competing risk. All-cause death will be analyzed using Kaplan–Meier methods, and survival curves will be compared using the log-rank test. Effect estimates for secondary time-to-event outcomes will also be presented as hazard ratios or subdistribution hazard ratios with 95% CIs, depending on the presence of competing risks. The exploratory end point will be analyzed descriptively.

Safety analyses will be conducted in all participants randomized and provided informed consent. Events occurring after initiation of the lipid-lowering therapy, including adverse events, adverse drug reactions, and serious adverse events, will be summarized by treatment group. Between-group differences will be assessed using appropriate statistical tests, such as chi-square or Fisher's exact tests. All statistical tests will be 2 sided, and a P value <0.05 will be considered statistically significant, unless otherwise specified.

Study Organization and Funding

The executive committee is responsible for ensuring compliance with the study protocol and ethical standards, supporting protocol refinement, guiding major trial-related decisions, and maintaining coordination among involved parties. The study is funded by Hanmi Pharmaceutical, which has no role in the design, conduct, data analysis, or interpretation of the trial.

DISCUSSION

Despite advances in lipid-lowering therapy for secondary prevention, current stroke guidelines disproportionately focus on atherosclerotic subtypes. Notably, these guidelines have been developed in the absence of randomized clinical trials exclusively enrolling patients with SVO stroke, underscoring a clear unmet need for evidence in this population. Rather than assuming uniform treatment effects across stroke causes, the SVO70 trial acknowledges that SVO has distinct pathophysiological and epidemiological characteristics that may influence the response to lipid-lowering therapy. Accordingly, it adopts a subtype-specific approach to LDL-C target setting, an area not addressed by existing guidelines.

A key strength of the SVO70 trial lies in its focused inclusion of patients with clearly defined SVO lesions, confirmed by neuroimaging and adjudicated by stroke neurologists. This approach enhances diagnostic accuracy and reduces the heterogeneity that has complicated interpretation in prior post hoc analyses. Both the sample size and end point definitions were tailored to reflect the relatively low vascular event rates characteristic of the population with SVO stroke. However,

Downloaded from http://ahajournals.org by on September 30, 2026

because the study will enroll only Asian participants—a group with a relatively higher prevalence of small vessel disease[9]—the generalizability of the findings must be interpreted by considering differences in small vessel disease burden across other ethnic and racial groups.

CONCLUSIONS

By prospectively evaluating lipid-lowering strategies in a rigorously selected cohort with SVO stroke, the SVO70 trial should provide relevant evidence to inform optimal LDL-C management in this underrepresented population. The results may support a more tailored approach to secondary prevention and contribute to future refinements in stroke care guidelines.

ARTICLE INFORMATION

Received September 25, 2025; accepted March 24, 2026.

Affiliations

Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea (W.Y., H.J.); Ewha Womans University Graduate Program in System Health Science and Engineering, Department of Neurology, Ewha Womans University Seoul Hospital, Ewha Womans University College of Medicine, Seoul, Korea (T-J.S.); Department of Neurology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Korea (S-H.K.); Department of Neurology, Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon, Korea (H.S.J.); Department of Neurology, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Korea (S-I.S.); Department of Neurology, Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul, Korea (Y.S.K.); Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea (B.J.K.); Department of Neurology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea (J-M.J.); Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea (K-H.J., J-M.K., E-J.L., M.C., S-H.L.); Department of Neurology, Kangwon National University Hospital, Kangwon National University College of Medicine, Chuncheon, Korea (S.K.); Department of Neurology, Inha University Hospital, Inha University College of Medicine, Incheon, Korea (H-K.P.); Department of Neurology, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea (S.Y.); Department of Neurology, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea (Y-J.C.); Department of Neurology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea (J-T.K.); Department of Neurology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea (Y.K.); Department of Neurology, Hallym University Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, Korea (C.K.); Department of Neurology, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Korea (H.Y.K.); Department of Neurology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea (M.S.O.); Department of Neurology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea (D-H.K.); Department of Neurology, Gil Medical Center, Gachon University College of Medicine, Incheon, Korea (Y-B.L.); Department of Neurology, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea (M-Y.E.); Department of Neurology, Wonkwang University Hospital, Wonkwang University School of Medicine, Iksan, Korea (H.Y.P.); Department of Neurology, Nowon Eulji Medical Center, Eulji University School of Medicine, Seoul, Korea (K.K.); Department of Neurology, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea (H-M.K.); Department of Neurology, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Korea (H-J.C.); Department of Neurology, Daejeon Eulji Medical Center, Eulji University School of Medicine, Daejeon, Korea (J.G.K.); Department of Neurology, Jeju National University Hospital, Jeju National University College of Medicine, Jeju, Korea (J.C.C.); Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea (J.Y.); Department of Neurology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (H.S.N.); Department of Neurology, National Health Insurance Service Ilsan Hospital, Ilsan, Korea (T.O.); Department of Neurology, Yeouido St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea (A-H.C.); Department of Neurology, National Medical Center, Seoul, Korea (J.Y.L.); Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Korea (J-Y.S.); Department of Neurology, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, Korea (J.H.P.); Department of Neurology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea (K-Y.P.); Department of Neurology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea (D-I.S.); Department of Neurology, Daegu Catholic University Medical Center, Daegu Catholic University School of Medicine, Daegu, Korea (Y.D.); Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Korea (Y.C.); Department of Neurology, Gyeongsang National University Changwon Hospital, Gyeongsang National University College of Medicine, Changwon, Korea (S.J.); Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (Y.H.J.); Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (W-K.S.); Department of Neurology, Dongguk University Ilsan Hospital, Dongguk University College of Medicine, Goyang, Korea (S-W.J.); Department of Neurology, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gwangmyeong, Korea (S.Y.H.); Department of Neurology, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Korea (S.J.A.); Department of Neurology, Chosun University Hospital, Chosun University College of Medicine, Gwangju, Korea (S.H.A.); and Department of Neurology, Kyungpook National University Hospital, Kyungpook National University School of Medicine, Daegu, Korea (Y-H.H.).

Sources of Funding

The study is funded by Hanmi Pharmaceutical, which has no role in the design, conduct, data analysis, or interpretation of the trial.

Disclosures

None.

Supplemental Material

SPIRIT Checklist

REFERENCES

1. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22. doi: 10.1016/S0140-6736(02)09327-3
2. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504. doi: 10.1056/NEJMoa040583
3. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559. doi: 10.1056/NEJMoa061894
4. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397. doi: 10.1056/NEJMoa1410489
5. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722. doi: 10.1056/NEJMoa1615664
6. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107. doi: 10.1056/NEJMoa1801174

Downloaded from http://ahajournals.org by on September 30, 2026

7. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2021;52:e364–e467. doi: 10.1161/STR.0000000000000375
8. Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Béjot Y, Cabrejo L, Cha JK, Ducrocq G, Giroud M, et al. A comparison of two LDL cholesterol targets after ischemic stroke. *N Engl J Med*. 2020;382:9–19. doi: 10.1056/NEJMoa1910355
9. Kim BJ, Kim JS. Ischemic stroke subtype classification: an asian viewpoint. *J Stroke*. 2014;16:8–17. doi: 10.5853/jos.2014.16.1.8
10. Yaghi S, Raz E, Yang D, Cutting S, Mac Grory B, Elkind MSV, de Havenon A. Lacunar stroke: mechanisms and therapeutic implications. *J Neurol Neurosurg Psychiatry*. 2021;92:823–830. doi: 10.1136/jnnp-2021-326308
11. Caplan LR. Lacunar infarction and small vessel disease: pathology and pathophysiology. *J Stroke*. 2015;17:2–6. doi: 10.5853/jos.2015.17.1.2
12. Bezerra DC, Sharrett AR, Matsushita K, Gottesman RF, Shibata D, Mosley TH Jr, Coresh J, Szklo M, Carvalho MS, Selvin E. Risk factors for lacune subtypes in the Atherosclerosis Risk in Communities (ARIC) study. *Neurology*. 2012;78:102–108. doi: 10.1212/WNL.0b013e31823efc42
13. Dib MJ, Zagkos L, Meena D, Burgess S, Chirinos JA, Gill D. LDL-c lowering, ischemic stroke, and small vessel disease brain imaging biomarkers: a Mendelian randomization study. *Stroke*. 2024;55:1676–1679. doi: 10.1161/STROKEAHA.123.045297
14. Xie Y, Liu S, Wang X, Huang H, Wang M, Qu W, Yu Z, Wang W, Luo X. Lipids, apolipoproteins, lipid-lowering drugs, and the risk of cerebral small vessel disease: a Mendelian randomization study. *J Am Heart Assoc*. 2024;13:e032409. doi: 10.1161/JAHA.123.032409
15. Hosomi N, Nagai Y, Kohriyama T, Nezu T, Maruyama H, Sunami N, Yokota C, Kitagawa K, Terayama Y, Takagi M, et al. The Japan Statin Treatment Against Recurrent Stroke (J-STARS): a multicenter, randomized, open-label, parallel-group study. *EBioMedicine*. 2015;2:1071–1078. doi: 10.1016/j.ebiom.2015.08.006
16. Duering M, Biessels GJ, Brodtmann A, Chen C, Cordonnier C, de Leeuw FE, Debette S, Frayne R, Jouvent E, Rost NS, et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol*. 2023;22:602–618. doi: 10.1016/S1474-4422(23)00131-X
17. Korean Society of Lipid and Atherosclerosis. *Korean guidelines for the management of dyslipidemia*. 5th ed. Seoul: Korean Society of Lipid and Atherosclerosis; 2022. Accessed August 31, 2025. https://lipid.or.kr/eng/pub/images/guidlines_2022.pdf
18. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, 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;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
19. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, de Backer GG, Delgado V, Ference BA, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188. doi: 10.1093/eurheartj/ehz455
20. Amarenco P, Benavente O, Goldstein LB, Callahan A 3rd, Sillesen H, Hennerici MG, Gilbert S, Rudolph AE, Simunovic L, Zivin JA, et al. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. *Stroke*. 2009;40:1405–1409. doi: 10.1161/STROKEAHA.108.534107
21. Statistics Korea. *Deaths by cause*. Accessed December 27, 2022. https://kosis.kr/eng.

Downloaded from http://ahajournals.org by on September 30, 2026