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Letter from the Editor

Despite the fact that stroke is a leading cause of disability among adults, there has been a shortage of high-quality studies to address such important issues as management of stroke risk factors. Well-documented risk factors include hypertension, diabetes mellitus, and hyperlipidemia. The optimal target blood pressure for secondary prevention of stroke is not well defined at present. It could vary according to patient age, comorbidities such as presence or absence of renal disease, and extent of cerebrovascular atherosclerosis. Similarly, until recently, no large randomized trial had evaluated two different low-density lipoprotein targets in patients with a recent ischemic stroke.

This collection of articles highlight some of the unresolved issues in stroke prevention. In the NEJM research article, Amarenco and colleagues compared target LDL cholesterol levels of <70 mg per deciliter and 90-110 mg per deciliter in patients with recent transient ischemic attack or ischemic stroke, finding a significant benefit in preventing subsequent cardiovascular events in the group treated to the lower target. NEJM Journal Watch summaries present highlights of research in patients with recent ischemic stroke or TIA, including consideration of optimal long-term blood pressure targets in these patients, investigation of the association of Ischemic stroke risk and lipoprotein (a) levels, and concluding with a review of various facets of secondary prevention after stroke. Clinicians must now take the next step and implement the results of these studies to optimize patient outcomes.

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A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

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ABSTRACT

BACKGROUND

The use of intensive lipid-lowering therapy by means of statin medications is recommended after transient ischemic attack (TIA) and ischemic stroke of atherosclerotic origin. The target level for low-density lipoprotein (LDL) cholesterol to reduce cardiovascular events after stroke has not been well studied.

METHODS

In this parallel-group trial conducted in France and South Korea, we randomly assigned patients with ischemic stroke in the previous 3 months or a TIA within the previous 15 days to a target LDL cholesterol level of less than 70 mg per deciliter (1.8 mmol per liter) (lower-target group) or to a target range of 90 mg to 110 mg per deciliter (2.3 to 2.8 mmol per liter) (higher-target group). All the patients had evidence of cerebrovascular or coronary-artery atherosclerosis and received a statin, ezetimibe, or both. The composite primary end point of major cardiovascular events included ischemic stroke, myocardial infarction, new symptoms leading to urgent coronary or carotid revascularization, or death from cardiovascular causes.

RESULTS

A total of 2860 patients were enrolled and followed for a median of 3.5 years; 1430 were assigned to each LDL cholesterol target group. The mean LDL cholesterol level at baseline was 135 mg per deciliter (3.5 mmol per liter), and the mean achieved LDL cholesterol level was 65 mg per deciliter (1.7 mmol per liter) in the lower-target group and 96 mg per deciliter (2.5 mmol per liter) in the higher-target group. The trial was stopped for administrative reasons after 277 of an anticipated 385 end-point events had occurred. The composite primary end point occurred in 121 patients (8.5%) in the lower-target group and in 156 (10.9%) in the higher-target group (adjusted hazard ratio, 0.78; 95% confidence interval, 0.61 to 0.98; P=0.04). The incidence of intracranial hemorrhage and newly diagnosed diabetes did not differ significantly between the two groups.

CONCLUSIONS

After an ischemic stroke or TIA with evidence of atherosclerosis, patients who had a target LDL cholesterol level of less than 70 mg per deciliter had a lower risk of subsequent cardiovascular events than those who had a target range of 90 mg to 110 mg per deciliter. (Funded by the French Ministry of Health and others; Treat Stroke to Target ClinicalTrials.gov number, NCT01252875.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Amarenco at the Department of Neurology and Stroke Center, Bichat Hospital, 46 rue Henri Huchard, Paris 75018, France, or at pierre.amarenco@aphp.fr.

*A complete list of the Treat Stroke to Target investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Elevated Lipoprotein(a) and Cardiovascular Disease: More Evidence of a Causal Link

Ischemic stroke risk was associated with Lp(a) levels and* LPA *gene variants in a contemporary Danish population study.

Lipoprotein(a) [Lp(a)] is increasingly recognized as an important risk factor for atherosclerosis. Lp(a) levels are primarily genetically determined and remain stable over time. Using data from the contemporary Copenhagen General Population Study (n=49,699) and the historical Copenhagen City Heart Study (n=10,813), investigators explored whether elevated Lp(a) is associated with increased risk for ischemic stroke. Additionally, they analyzed potential links between stroke risk and two *LPA* genotype variants (*LPA* KIV-2 number of repeats and presence of *LPA* rs10455872).

In the contemporary cohort, individuals with the highest Lp(a) levels (>93 mg/dL) had 1.6 times the adjusted risk for ischemic stroke as those with the lowest levels (<10 mg/dL). Each 50 mg/dL increase in Lp(a) level corresponded to a hazard ratio for ischemic stroke of 1.20 in observational analyses and 1.20 and 1.27 in the two genetic analyses. The highest absolute risk for stroke was found in individuals older than 70 who were active smokers and had hypertension.

In the historical cohort, the results were directionally similar but did not reach statistical significance.

COMMENT

The independent association of Lp(a) with ischemic stroke risk is unsurprising and adds to the growing body of evidence supporting a causal link between Lp(a) and cardiovascular disease. As the authors note, the study cannot be generalized to other populations, including African-Americans, who are known to have higher Lp(a) levels. Although we do not yet have drugs that effectively lower Lp(a) and reduce adverse cardiovascular outcomes, high Lp(a) values should prompt more-intensive treatment of other modifiable cardiovascular risk factors.

— Fatima Rodriguez, MD, MPH, FACC, FAHA

Langsted A et al. Elevated lipoprotein(a) and risk of ischemic stroke. **J Am Coll Cardiol** *2019 Jul 9; 74:54. (https://doi.org/10.1016/j.jacc.2019.03.524)*

Long-Term Blood Pressure Goals After Stroke: A Randomized Trial

The incidence of recurrent stroke was not significantly lower when a systolic BP target of 120 mm Hg was used, compared with a higher target.

In the only large randomized trial in which researchers compared two blood pressure (BP) goals for long-term secondary prevention after stroke (<130 vs. 130–149 mm Hg), the incidence of recurrent stroke was not significantly lower with more-intensive treatment (*Lancet* 2013; 382:507). Now, in a study from Japan, nearly 1300 patients with recent stroke (85% ischemic, 15% hemorrhagic) and BP >130/80 mm Hg were randomized to a long-term target of <120/80 mm Hg or <140/90 mm Hg. Most patients had received hypertension treatment prior to their strokes. The study included a stepwise protocol for drug titration.

During mean follow-up of 4 years, average systolic BP was significantly lower with more-intensive than with less-intensive treatment (126.7 vs. 133.2 mm Hg); diastolic BP was 77 mm Hg in both groups. However, a difference in incidence of recurrent stroke was not statistically significant (6.2% and 8.2%; P=0.15). In subgroup analysis, incidence of intracerebral hemorrhage was lower in the more-intensively treated group (0.2% vs. 1.7%; P=0.02), but ischemic stroke incidence was similar (6.0% and 6.5%; P=0.69).

COMMENT

In this trial, lowering systolic BP to <130 mm Hg did not reduce the overall incidence of recurrent stroke. However, when these results are pooled with results from the other large trial (cited above), a small reduction in recurrent stroke (≈1.5 percentage points during 4 years) reaches statistical significance. I believe that a ≈120 mm Hg systolic BP target for patients with previous stroke is reasonable if it can be accomplished without adverse effects. However, the incremental benefit likely is small, and whether the outcomes from Japan are applicable to other populations is unclear. ***— Allan S. Brett, MD***

Kitagawa K et al. Effect of standard vs intensive blood pressure control on the risk of recurrent stroke: A randomized clinical trial and meta-analysis. **JAMA Neurol** *2019 Nov; 76:1309. (https://doi.org/10.1001/jamaneurol.2019.2167)*

Secondary Prevention After Stroke

Researchers examined lipid targets, blood pressure targets, and antithrombotic therapy after embolic stroke of unknown source.

In 2019, data were published from three large randomized trials in which several facets of secondary prevention after stroke were examined.

One trial addressed antithrombotic therapy to prevent recurrence in patients with embolic stroke of unknown source (ESUS). About 5400 patients with ESUS received either dabigatran or aspirin; during average follow-up of 19 months, researchers noted no significant difference in incidence of recurrent stroke in the two groups (*NEJM JW Gen Med* Aug 1 2019 and *N Engl J Med* 2019; 380:1906). In a similar study, published in 2018, investigators compared rivaroxaban and aspirin and reached a similar conclusion — no difference between groups (*NEJM JW Gen Med* Jun 15 2018 and *N Engl J Med* 2018; 378:2191). Thus, although the idea of anticoagulation rather than antiplatelet therapy for ESUS patients is intriguing, trial results don't support that move.

The widely prescribed fixed dose of 80-mg atorvastatin for secondary stroke prevention comes from a single trial (SPARCL) published in 2006 (*N Engl J Med* 2006; 355:549). The 80-mg atorvastatin dose reduced the incidence of recurrent stroke from 13% to 11% during 5 years of follow-up, but the result was barely statistically significant. In 2019, another group examined lipid-lowering therapy in nearly 3000 patients with recent ischemic stroke or transient ischemic attack (TIA) of presumed atherosclerotic origin. Patients were randomized to an LDL cholesterol target of <70 mg/dL or 90 to 110 mg/dL; treating physicians were permitted to use any statin and to add ezetimibe if necessary. During average follow-up of 3.5 years, incidence of the primary endpoint (including both recurrent stroke and coronary events) was slightly lower in the lower-target group (8.5% vs. 10.9%; P=0.04). These results support more flexibility in choosing lipid-lowering therapy after ischemic stroke; many patients in the lower-target group required only moderate-intensity statins (*NEJM JW Gen Med* Dec 15 2019 and *N Engl J Med* 2019 Nov 18; [e-pub]).

Finally, what is the optimal long-term blood pressure target in patients with recent stroke or TIA? In a Japanese study, 1300 patients were randomized to long-term targets of either <120/80 mm Hg or <140/90 mm Hg (*NEJM JW Gen Med* Dec 15 2019 and *JAMA Neurol* 2019; 76:1309). During 4 years of follow-up, a small difference in incidence of recurrent stroke did not reach significance (6% and 8%; P=0.15). In the only previous large trial in which this question was examined directly (but conducted exclusively in patients with lacunar stroke), results were similar — a small but nonsignificant reduction in recurrent stroke in a lower-target group (*Lancet* 2013; 382:507). My take: A target of roughly 120 mm Hg is reasonable, as long as the patient tolerates treatment without adverse effects.

— Allan S. Brett, MD