to be an important aspect of the NEJM Catalyst mission. These events and webcasts will remain free for all viewers. The NEJM Catalyst Insights Council, which has grown and matured into a valuable sounding board on important topics in care delivery for clinicians, clinical leaders, and health care executives, will be prominent in *NEJM Catalyst Innovations in Care Delivery*. Insights Council membership will be expanded to incorporate international viewpoints.

Although the bulk of journal content will be available only to subscribers, select articles and interviews will be open to all.

Like much in health care delivery today, NEJM Catalyst represents a new type of work, aimed at problems that are new to our times. We look forward to your input, and we hope that *NEJM Catalyst Innovations in Care Delivery* will play a valuable role in accelerating the movement toward higher-value health care systems.

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Statins and Stroke — It's Complicated

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Elevated levels of cholesterol are a well-known risk factor for cardiovascular disease, including stroke, and efforts to lower cholesterol levels to reduce risk have been ongoing for decades. Because of their dramatic effect on cholesterol, statins have been widely prescribed to prevent cardiovascular events in patients at high risk. Most trials of primary and secondary prevention with statins have shown a decrease in the incidence of vascular events,[1] and statins are now the essential component of medical management in patients at risk for cardiovascular disease. Although statins were designed to reduce cholesterol levels, the ideal use of these agents and the mechanism by which they protect against cardiovascular events have been a source of controversy. Statins have pleiotropic properties that may mediate some or all of their benefits.[2] Evidence also suggests that statins may exert a neuroprotective effect and improve recovery after stroke.[3]

However, many questions remain about the use of statins. What is the most effective dose and which target cholesterol level is to be achieved with statin therapy? Which component of cholesterol is most important to measure? Should we target a percentage reduction or a particular numerical level or use a standard statin dose? In addition to the beneficial effects of statins, studies have suggested that aggressive cholesterol reduction may increase the risk of hemorrhagic stroke and cause systemic side effects. Thus, the seemingly simple task of reducing cholesterol levels and thereby protecting against cardiovascular events has turned into a complex web of uncertainties about mechanism, dose, and targets.

Most trials of statin therapy have enrolled patients with cardiovascular disease or those at high risk for vascular events. In contrast, in the influential SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial[4] in 2006, investigators enrolled only patients with previous stroke or transient ischemic attack (TIA) and a moderate elevation in low-density lipoprotein (LDL) cholesterol (100 to 190 mg per deciliter [2.6 to 4.9 mmol per liter]) and randomly assigned them to receive either high-intensity statin treatment (atorvastatin at a dose of 80 mg) or placebo.[4] At 5 years, the patients who received atorvastatin had an absolute risk of subsequent stroke that was 2.2 percentage points lower than that in the placebo group, an absolute risk of major cardiovascular events that was 3.5 percentage points lower, and a nonsignificantly higher number of hemorrhagic strokes.

On the basis of this trial, guidelines have recommended treatment with high-intensity statins in patients with stroke caused by atherosclerosis.[5] However, some clinicians prefer to adjust the statin dose on the basis of the LDL cholesterol level and to administer statins to all patients

with stroke regardless of mechanism. Since the SPARCL investigators used a single high dose of atorvastatin, it is uncertain whether the observed benefit was due to a reduction in the cholesterol level or to other effects of atorvastatin. Subgroup analysis from the SPARCL trial[6] and a subsequent meta-analysis[7] suggested a greater benefit with lower levels of LDL cholesterol. In a post hoc analysis of the SPARCL data, patients with an LDL cholesterol level of less than 70 mg per deciliter (1.8 mmol per liter) had a relative risk of stroke that was 28% lower than that in patients with an LDL cholesterol level of more than 100 mg per deciliter.[6]

Amarenco et al. now report in the *Journal* the results of the Treat Stroke to Target trial,[8] in which they randomly assigned patients with stroke or TIA to receive statin therapy with or without ezetimibe, targeting a range of LDL cholesterol of 90 mg to 110 mg per deciliter (higher-target group), or to receive more aggressive treatment with a target level of LDL cholesterol of less than 70 mg per deciliter (lower-target group). The composite primary end point was a major cardiovascular event, which included ischemic stroke, myocardial infarction, new symptoms leading to urgent coronary or carotid revascularization, or death from cardiovascular causes.

At a median of 2.7 years, approximately 30% of the patients had discontinued therapy, although the mean levels of LDL cholesterol in the two groups were within the desired targets. After a median follow-up of 3.5 years, the primary end point had occurred in 8.5% of the patients in the lower-target group and in 10.9% of those in the higher-target group (hazard ratio, 0.78; 95% confidence interval, 0.61 to 0.98; P=0.04). Since the primary end point included coronary events as well as stroke (unlike the population in the SPARCL trial), no conclusion could be reached regarding between-group differences regarding stroke alone. Fortunately, there was no significant between-group difference in the incidence of intracranial hemorrhage in this trial. Unfortunately, the trial was stopped early because of a lack of funding.

Despite the limitations of this trial, the results could help to guide clinicians in the use of statins in patients with cardiovascular disease who have had strokes. The trial provides evidence to support the original concept of statins as an agent to reduce cardiovascular risk, primarily by reducing cholesterol levels. Is LDL cholesterol the only and best target to reach this goal? That question is subject to further study to fine-tune our approach in terms of risks and benefits. Although the pleiotropic effects of statins may also be dose-dependent, it seems practical to focus on LDL cholesterol as the target for most patients with atherosclerotic mechanisms of stroke. The potential harm of hemorrhage with aggressive cholesterol reduction is also worthy of additional study. Other issues to be explored include whether patients with nonatherosclerotic mechanisms of stroke benefit from low-target LDL cholesterol levels and what is the best treatment for patients with stroke who have very high LDL cholesterol levels. The issue of how to use statins to reduce cardiovascular risk remains complicated, just a little less so.

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