EDITORIAL

SCIENCE BEHIND THE STUDY

Bempedoic Acid and the Prevention of Cardiovascular Disease

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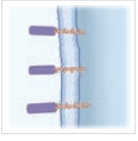
In an article now published in the *Journal*, Nissen and colleagues report the results of the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) Outcomes trial, which tested the effect of bempedoic acid in patients with or at increased risk for cardiovascular disease.[1] Patients who were unable or unwilling to take high-intensity statins because of unacceptable adverse effects ("statin-intolerant" patients) were the target trial population; statins are typically used as first-line agents to prevent cardiovascular events in patients at high cardiovascular risk. Nissen et al. found that the percent reduction in the LDL cholesterol level was 21 percentage points greater with bempedoic acid than with placebo. This reduction in cholesterol level corresponded to a 13% lower risk of major adverse cardiovascular events, defined as a four-component composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. These results are discussed in an accompanying editorial[2] and are welcome news for a patient population in which it is otherwise very challenging to achieve meaningful reductions in cholesterol levels and the risk of cardiovascular events.

Key Concepts

Prodrug

A therapeutic agent that is delivered in an inactive form and is metabolized to its active form in vivo.



Protein prenylation

The addition of farnesyl or geranygeranyl moieties (both of which are hydrophobic) to proteins, which facilitates their attachment to membranes.

An expanded illustrated glossary is available at NEJM.org

HOW DO STATINS WORK?

Statins derive their name from lovastatin, the first commercially available inhibitor of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of the mevalonate pathway that is responsible for cholesterol and isoprenoid synthesis (Fig. 1). Because most cholesterol is derived from intracellular synthesis rather than from the diet, statins produce intracellular cholesterol depletion. As a compensatory response, cholesterol-depleted cells up-regulate low-density lipoprotein (LDL) receptors on the cell surface to internalize more cholesterol for cellular needs (Fig. 1). In the liver, this process affords increased removal of cholesterol-rich LDL particles from the circulation, which explains the LDL cholesterol–lowering effect of statins. The more potent drugs of this class, at the highest doses, can lower the LDL cholesterol level in the blood by 30 to 50% and have profound benefits in both the primary and secondary prevention of cardiovascular disease.[3] As a consequence, statins as a class are among the most widely used drugs in the world.

The inhibition of HMG-CoA reductase has implications beyond cholesterol synthesis. This enzyme is also required for the isoprenoid pathway, which is needed for the synthesis of ubiquinol (a form of coenzyme Q that is involved in cellular energy production), and post-translational

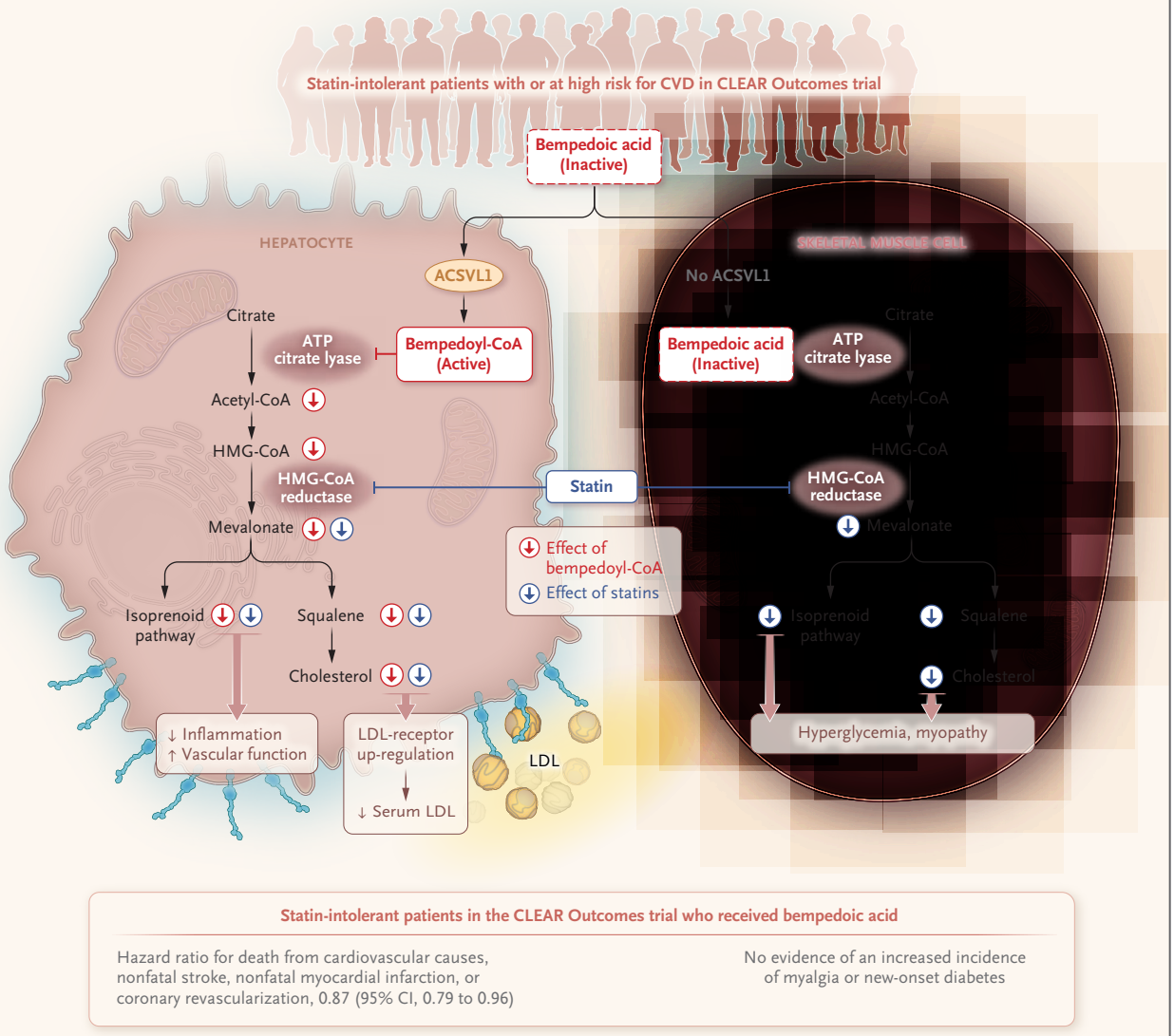


Figure 1. Targeting the Low-Density Lipoprotein (LDL) Cholesterol Synthesis Pathway.

Nissen et al.[1] report the cardiovascular outcomes with bempedoic acid, an ATP citrate lyase inhibitor, in statin-intolerant patients who had or were at high risk for cardiovascular disease. ATP citrate lyase lies upstream of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA), the enzyme targeted by the statins; it is a reasonable target for treatment in statin-intolerant patients, all the more so because such patients often have statin-induced myopathy. Because very-long-chain acyl-CoA synthetase 1 (ASCVL1) is required to activate bempedoic acid — and ASCVL1 is not expressed in skeletal muscle — bempedoic acid may remain inactive in skeletal muscle, which could reduce the risk of myopathy.

protein prenylation (see Key Concepts), which is essential for the cell-membrane attachment and function of many signaling proteins, such as the Ras and Rho families of guanosine triphosphatases that are critical for cell adhesion and migration, respectively. Given the ubiquitous expression of HMG-CoA reductase, it is not surprising that the use of statins could have important implications for cellular functions in many tissues. Indeed, this noncholesterol component of

the mevalonate pathway is thought to underlie favorable "pleiotropic" effects of statins, such as reduced inflammation and enhanced vascular function, as well as undesirable effects of statins, such as elevated blood sugar levels and myopathy.

On balance, statins have a very favorable therapeutic window, with the benefits far outweighing the risks. However, the ultimate benefit of statins can be limited by discontinuation of therapy because of unacceptable adverse effects; statin-associated muscle symptoms are the most common cause of discontinuation. The actual prevalence of statin intolerance is a topic of debate, but a recent meta-analysis places the overall rate at approximately 9%.[4] Conditions such as older age, obesity, diabetes, chronic liver disease, and chronic kidney disease appear to increase the risk.

HOW DOES BEMPEDOIC ACID WORK?

Bempedoic acid is a prodrug: it requires conversion by the very-long-chain acyl-CoA synthetase 1 (ASCVL1) into a CoA-thioester that is the active metabolite. The CoA-thioester inhibits adenosine triphosphate citrate lyase that is in the cholesterol biosynthetic pathway upstream of HMG-CoA reductase (Fig. 1). Thus, through a mechanism distinct from that of statins, bempedoic acid inhibits the mevalonate pathway and produces a depletion of cellular cholesterol and subsequent up-regulation of hepatic LDL receptors to lower circulating LDL cholesterol levels.

Therapy with bempedoic acid has theoretical advantages over the use of statins. Because bempedoic acid is a prodrug, it should be active only in tissues that express ASCVL1. Liver contains abundant ASCVL1 and thus facilitates cholesterol lowering by bempedoic acid; muscle tissue, however, does not express ASCVL1. Thus, bempedoic acid may offer an advantage over statins in the avoidance of myopathic symptoms or hyperglycemia, because bempedoic acid would not be expected to inhibit cholesterol or isoprenoid synthesis in muscle.

IS IT PREFERABLE TO USE STATINS FOR CARDIOVASCULAR DISEASE?

Currently, statins have an enviable track record in preventing both first and subsequent occurrences of cardiovascular disease. It is generally accepted that contemporary statins produce a 22% reduction in the risk of vascular events for each reduction in the LDL cholesterol level of 39 mg per deciliter (1 mmol per liter) and that this response is roughly linear.[3] It is also accepted that high-intensity statin treatment (i.e., ≥20 mg of rosuvastatin or ≥40 mg of atorvastatin) should yield a reduction in the LDL cholesterol level of approximately 50%. Thus, it is clear that a considerable reduction in the risk of cardiovascular events can be achieved with statin monotherapy.

Bempedoic acid monotherapy lowers the LDL cholesterol level up to 28%,[5] and this effect is attenuated to approximately 16% in patients receiving the maximum tolerated dose of statins.[6] Although we do not have specific cardiovascular outcome data with bempedoic acid monotherapy, it is associated with a reduction in the level of C-reactive protein, a well-established biomarker for future cardiovascular events. The CLEAR Outcomes trial also showed that bempedoic acid, used in addition to modest cholesterol-lowering therapy, led to a reduction in the LDL cholesterol level that exceeded that with placebo by 29 mg per deciliter (0.75 mmol per liter), a finding that corresponded to a 13% lower risk of cardiovascular disease. This correspondence between a reduction in the LDL cholesterol level and a reduction in the risk of cardiovascular events is on par with that observed for statins. However, determining whether bempedoic acid is preferable to statins would require a direct-comparison trial, which is unlikely to be realized with patients who are able to receive statins, given that it would be unethical to withhold statin treatment from them. Rather, the most likely situation in which a choice would need to made between bempedoic acid and statins would be for the treatment of patients with statin-associated adverse effects such as myopathy or diabetes, which could, in theory, be avoided with bempedoic acid.

ANYTHING NOTABLE ABOUT SIDE EFFECTS?

The absence of ASCVL1 in many peripheral tissues brought hope that therapy with bempedoic acid could avoid any of the peripheral side effects, such as diabetes and myopathy, that are known to be associated with statins. The data from the CLEAR Outcome trial did not show a clear association between bempedoic acid and muscle disorders, new-onset diabetes, or worsening hyperglycemia[1] — welcome news for statin-

intolerant patients. However, these data must be interpreted cautiously, because bempedoic acid, when combined with a statin, appears to enhance the occurrence of muscle symptoms.[6,7] Moreover, bempedoic acid has its own reported side effects, including tendon rupture, increased uric acid levels, gout, and reduced glomerular filtration rate, which are not seen with statin use. In terms of drug interactions, bempedoic acid can increase the circulating levels of simvastatin and pravastatin, so it should not be used in patients who are receiving these agents at doses above 20 mg and 40 mg, respectively. Similarly, bempedoic acid should not be used with fibrates other than fenofibrate because of concerns regarding cholelithiasis.

WHERE DOES BEMPEDOIC ACID FIT IN WITH OTHER CHOLESTEROL-LOWERING TREATMENTS?

Available data clearly indicate that bempedoic acid can be used as an adjunct to statin and nonstatin therapies (except as noted above) to produce an additional 16 to 26% reduction in the LDL cholesterol level. However, it is not yet clear to what extent adjunctive bempedoic acid will further reduce the risk of cardiovascular events. This issue can only be addressed with specific trials powered to detect the effect of bempedoic acid on clinical events. However, at least in statin-intolerant patients, data from the CLEAR Outcomes trial indicate that bempedoic acid may reduce both the LDL cholesterol level and the risk of cardiovascular events.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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