EDITORIAL

Benefits of Bempedoic Acid — Clearer Now

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Vascular atherosclerosis begins in young adulthood and progresses over decades. The condition is associated with considerable morbidity and mortality from coronary, cerebrovascular, and peripheral vascular disease. The foundation of contemporary prevention and treatment of atherosclerosis is lowering the serum cholesterol level with 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (statins). Statins reduce the low-density lipoprotein (LDL) cholesterol level, slow the progression of atherosclerosis, and reduce the morbidity and mortality associated with coronary, cerebrovascular, and peripheral vascular events.[1] High-intensity statin therapy is recommended for all patients with established atherosclerotic vascular disease, as well as those at high risk for atherosclerotic vascular disease.[2] Unfortunately, a sizable percentage (approximately 10%) of those who would benefit from statins are unable or unwilling to take them, primarily owing to muscle-related symptoms.[3,4]

Fortunately, alternative LDL cholesterol–lowering therapies, such as ezetimibe, proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, and bempedoic acid, are available.[5-7] Ezetimibe has a modest effect in lowering the LDL cholesterol level and the risk of cardiovascular events, and PCSK9 inhibitors, although they are highly effective at lowering the LDL cholesterol level, require parenteral administration and are expensive. Bempedoic acid, an inhibitor of ATP citrate lyase, works upstream of statins in the same mechanistic pathway and reduces the LDL cholesterol level when used alone or in combination with ezetimibe in statin-intolerant patients or with statins or ezetimibe in patients with familial hypercholesterolemia.[8-10] Bempedoic acid is a prodrug that is metabolized to its active metabolite in the liver but not in peripheral tissues and thus has few, if any, muscle-related side effects.[9] What has been lacking to date is high-quality evidence that bempedoic acid reduces the risk of clinical events.

In an article now published in the *Journal*, Nissen et al. begin to fill this gap with the results of the CLEAR (Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen) Outcomes trial.[11] A total of 13,970 patients who had or were at high risk for atherosclerotic vascular disease and were unable to take more than a very low dose of a statin were randomly assigned to receive bempedoic acid (180 mg daily) or placebo. The percent reduction in the LDL cholesterol level was greater with bempedoic acid than with placebo by 21 percentage points, and the risk of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization (the primary composite end point) was 13% lower with bempedoic acid than with placebo over a median of 3.4 years. Bempedoic acid also reduced the risk of secondary end-point events, including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (a three-component composite), fatal or nonfatal myocardial infarction, and coronary revascularization. Similar effects of bempedoic acid were seen in patients using concomitant ezetimibe and very-low-dose statins. Interestingly, a numerically greater effect of bempedoic acid on the primary end point was observed for the 30% of patients in the primary-prevention cohort than for the 70% of patients in the secondary-prevention co-

hort. The percentage of patients with myalgias was similar in the bempedoic acid group and the placebo group, but incidences of gout, cholelithiasis, and laboratory elevations in creatinine, uric acid, and hepatic enzyme levels were higher with bempedoic acid than with placebo.

The compelling results of the CLEAR Outcomes trial will and should increase the use of bempedoic acid in patients with established atherosclerotic vascular disease and in those at high risk for vascular disease who are unable or unwilling to take statins. It is premature, however, to consider bempedoic acid as an alternative to statins. Given the overwhelming evidence of the vascular benefits of statins, clinicians should continue their efforts to prescribe them at the maximum tolerated doses for appropriate patients, including those who may have discontinued statins because of presumed side effects.[4] Although bempedoic acid also reduces the LDL cholesterol level in patients taking statins, the clinical benefits of bempedoic acid added to standard statin therapy are unknown.[8]

Two observations from the CLEAR Outcomes trial warrant further exploration. First, given the pathobiology of atherosclerosis, the suggestion of a greater effect of bempedoic acid in the primary-prevention cohort than in the secondary-prevention cohort is probably due to chance. It is plausible, however, that patients benefit more from bempedoic acid administered early in the course of atherosclerotic disease or that concomitant therapies diminished the benefit of bempedoic acid in the secondary-prevention cohort. Second, bempedoic acid had no observed effect on mortality. As the investigators note, this finding could be due to effective concomitant therapy, treatment and observation periods that were too short, or the actual absence of an effect of bempedoic acid on mortality. Many individual trials of statins have also not shown an effect of the agent on mortality; it was only through the meta-analysis of multiple clinical trials that the effects of statins on mortality became clear.

Bempedoic acid has now entered the list of evidence-based alternatives to statins for primary and secondary prevention in patients at high cardiovascular risk. The benefits of bempedoic acid are now clearer, and it is now our responsibility to translate this information into better primary and secondary prevention for more at-risk patients, who will, as a result, benefit from fewer cardiovascular events.

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

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This editorial was published on March 4, 2023, at NEJM.org.

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DOI: 10.1056/NEJMe2301490