I can see CLEAR-ly now the LDL is down

Atherosclerotic cardiovascular disease (ASCVD), a consequence of elevated LDL-cholesterol levels, is associated with considerable morbidity and mortality. The cornerstone of its prevention and treatment is the lowering of LDL-cholesterol levels through the high-intensity use of statins. However, a sizeable percentage of those who would benefit from statins report side-effects from their use. The CLEAR Outcomes trial aimed to establish the effects of bempedoic acid, an alternative LDL-cholesterol-lowering agent, on cardiovascular outcomes in a cohort at high risk of ASCVD, but unable or unwilling to take optimal doses of statins for primary or secondary prevention. A 21.1% greater reduction in LDL-cholesterol was recorded in those receiving bempedoic acid compared with placebo. The primary composite endpoint of four-point major adverse cardiovascular events was significantly reduced by 13% with bempedoic acid over a median follow-up of 40.6 months. It also reduced the risk of secondary endpoint events. While bempedoic acid is not a substitute for a statin, and despite higher incidences of some adverse effects, these results suggest that it is a viable alternative for statin-intolerant individuals.

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Elevated LDL-cholesterol levels are a proven direct cause of atherosclerotic cardiovascular disease (ASCVD) and mortality. Contemporary lipid guidelines, such as the 2019 ESC/EAS recommendations (Mach et al, 2020), have driven down LDL-cholesterol targets for people at highest CV risk; for secondary prevention in very high-risk people, an LDL-cholesterol reduction of ≥50% from baseline **and** an LDL-cholesterol target of <1.4 mmol/L are now recommended.

Moreover, for every 1 mmol/L reduction in LDL-cholesterol, there is a 22% reduction in the annual rate of major vascular events (Cholesterol Treatment Trialists' Collaboration et al, 2010). Furthermore, there was no evidence of any threshold within the cholesterol target range studied, suggesting that reducing LDL-cholesterol by 2–3 mmol/L would reduce annual CV risk by up to 50%.

Statins are the cornerstone of CV risk reduction strategies, and we can expect around a 50% reduction in LDL-cholesterol with a high-intensity statin approach, such as atorvastatin 40 mg. However, the "rule of 6" tells us the response to dose increase of a statin is not proportional and, in general, doubling a statin dose above the minimally effective dose reduces LDL-cholesterol by only an additional 6% (Knopp, 1999). Therefore, for many of our patients at the highest CV risk, statins alone will be inadequate to achieve these tighter LDL-cholesterol targets.

Whilst it is increasingly accepted that most side-effects attributed to statins are due to a "nocebo" effect (an expectation of adverse side effects, rather than actual adverse events *per se*), it is estimated that around 9% of patients are truly statin-intolerant (Bytyçi et al, 2022). These individuals remain at significant risk of a future major adverse CV event (MACE) and would benefit from alternative LDL-cholesterol-lowering therapy.

Bempedoic acid is a newer addition to our armamentarium to lower LDL-cholesterol. It is a pro-drug that inhibits liver cholesterol synthesis upstream of statins. However, bempedoic acid is activated in the liver, and not peripheral muscle, and therefore is not associated with significant muscle-related adverse effects. The phase 3 clinical trial programme investigating bempedoic acid has demonstrated 17–28% reductions in LDL-cholesterol with bempedoic acid alone, and a 38% reduction when used in combination with ezetimibe (Ballantyne, 2020). In the clinical trial programme, bempedoic acid was generally well

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"The results of CLEAR Outcomes position bempedoic acid as a compelling, evidence-based alternative to statins for statin-intolerant individuals, with an associated significant reduction in cardiovascular morbidity."

tolerated. However, more commonly reported adverse effects included hyperuricaemia, pain in extremities, anaemia and constipation. The CV benefits of bempedoic acid have, hitherto, to be elucidated.

The CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen) Outcomes trial – the CV outcomes trial for bempedoic acid – was presented at a late-breaking session of the American College of Cardiology annual meeting in early March 2023, and simultaneously published in the *New England Journal of Medicine* (Nissen et al, 2023).

CLEAR Outcomes was a double-blind, randomised, placebo-controlled trial that recruited 13 970 individuals who were unable or unwilling to take optimal doses of statins due to intolerable side-effects (i.e. "statin-intolerant" individuals) and who had established, or were at high risk of, ASCVD.

Mean LDL-cholesterol at baseline was 3.59 mmol/L. Mean age was 65.5 years, with an impressive 48.2% female participants (who are known to have a higher prevalence of statin intolerance than males [Karalis et al, 2016]), and 45.6% had a background of diabetes. Over two thirds of the population had a history of a previous CV event (i.e. secondary prevention was clinically indicated) and just over a fifth of participants were taking a non-optimal dose of statin. Of the trial population, 11.5% were taking ezetimibe. Disappointingly, over 90% of the trial population was White, making it challenging to extrapolate these results to other races.

Participants received 180 mg of oral bempedoic acid or placebo and were followed up for a mean duration of 40.6 months. The primary endpoint of the trial was 4-point MACE: a composite of death from CV causes, non-fatal myocardial infarction, non-fatal stroke and coronary revascularisation.

After 6 months of follow-up, mean LDL-cholesterol levels were 2.77 mmol/L in the bempedoic acid group, compared with 3.52 mmol/L in the placebo group. Thus, bempedoic acid reduced mean LDL-cholesterol levels by 21.1% over 6 months.

Interestingly, after 6 months, there was also a 21.6% reduction in median high-sensitivity CRP (hsCRP) level with bempedoic acid. It is well established that hsCRP is a reliable early indicator of inflammation, atherosclerosis and CVD in asymptomatic patients.

The primary endpoint of the study was significantly reduced by 13% with bempedoic acid. Absolute risk reduction was 1.6%, equating to a number needed to treat of 63 over 40 months to prevent one composite event.

There were also significant reductions in key secondary endpoints of 3-point MACE (15% relative risk reduction [RRR]), fatal or non-fatal myocardial infarction (23% RRR) and coronary revascularisation (19% RRR).

Of note, there was no significant reduction observed in fatal or non-fatal stroke, CV mortality or all-cause mortality.

Interestingly, prespecified subgroup analyses suggested that the primary prevention cohort of the trial population had a more significant reduction in the composite endpoint with bempedoic acid compared to the secondary prevention cohort, but, of course, this finding can only be hypothesis-generating.

With regard to adverse events, reassuringly, there was no significant difference between bempedoic acid and placebo with respect to myalgia, rhabdomyolysis, worsening hyperglycaemia or new-onset diabetes, neurocognitive disorders or malignancies. These are all adverse effects that have been associated with statins in the past.

Of note, there were significant differences observed with bempedoic acid for raised liver enzymes (4.5% vs 3.0%) and renal impairment (11.5% vs 8.6%). Additionally, there were imbalances noted in the incidence of hyperuricaemia (10.9% vs 5.6%), gout (3.1% vs 2.1%) and gallstones (2.2% vs 1.2%). The latter finding has not been observed previously with bempedoic acid.

The results of CLEAR Outcomes position bempedoic acid as a compelling, evidence-based alternative to statins for statin-intolerant individuals, with an associated significant reduction in CV morbidity. These results are consistent with the LDL hypothesis: that elevated LDL-cholesterol is a causal factor in the development of ASCVD. However, bempedoic

acid should not be considered a substitute for statins, with their potent LDL-cholesterol-lowering efficacy, established mortality benefits and associated beneficial CV pleiotropic effects.

Overall, the adverse effect profile of bempedoic acid is reassuring and, helpfully, markedly different from statins. However, the reported adverse effects do suggest that it would be prudent to undertake regular, albeit infrequent, blood monitoring after initiation of bempedoic acid.

In conclusion, CLEAR Outcomes provides a clearer role for bempedoic acid in the primary and secondary prevention of ASCVD, and should drive redesign in statin intolerance pathways. ■

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Nissen SE, Lincoff AM, Brennan D et al; CLEAR Outcomes Investigators (2023) Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med* 4 Mar [Epub ahead of print]

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ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

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ABSTRACT

BACKGROUND

Bempedoic acid, an ATP citrate lyase inhibitor, reduces low-density lipoprotein (LDL) cholesterol levels and is associated with a low incidence of muscle-related adverse events, its effects on cardiovascular outcomes remain uncertain.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial involving patients who were unable or unwilling to take statins owing to unacceptable adverse effects ("statin-intolerant" patients) and had, or were at high risk for, cardiovascular disease. The patients were assigned to receive oral bempedoic acid, 180 mg daily, or placebo. The primary end point was a four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

RESULTS

A total of 13,970 patients underwent randomization; 6992 were assigned to the bempedoic acid group and 6978 to the placebo group. The median duration of follow-up was 40.6 months. The mean LDL cholesterol level at baseline was 139.6 mg per deciliter in both groups, and after 6 months, the reduction in the level was greater with bempedoic acid than with placebo by 29.2 mg per deciliter; the observed difference in the percent reductions was 21.1 percentage points in favor of bempedoic acid. The incidence of a primary end-point event was significantly lower with bempedoic acid than with placebo (819 patients [11.7%] vs. 927 [13.3%]; hazard ratio, 0.87; 95% confidence interval [CI], 0.79 to 0.96; P=0.004), as were the incidences of a composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction (575 [8.2%] vs. 663 [9.5%]; hazard ratio, 0.85; 95% CI, 0.76 to 0.96; P=0.006), fatal or nonfatal myocardial infarction (261 [3.7%] vs. 334 [4.8%]; hazard ratio, 0.77; 95% CI, 0.66 to 0.91; P=0.002), and coronary revascularization (435 [6.2%] vs. 529 [7.6%]; hazard ratio, 0.81; 95% CI, 0.72 to 0.92; P<0.001). Bempedoic acid had no significant effects on fatal or nonfatal stroke, death from cardiovascular causes, and death from any cause. The incidences of gout and cholelithiasis were higher with bempedoic acid than with placebo (3.1% vs. 2.1% and 2.2% vs. 1.2%, respectively), as were the incidences of small increases in serum creatinine, uric acid, and hepatic-enzyme levels.

CONCLUSIONS

Among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization). (Funded by Esperion Therapeutics; CLEAR Outcomes ClinicalTrials.gov number, NCT02993406.)