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Review Article

Is Bempedoic acid effective for secondary prevention of cardiovascular disease?

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Abstract

Bempedoic acid is a cholesterol-lowering drug approved for reduction of the risk of myocardial infarction (MI) and coronary revascularization in adults who are unable to take recommended statin therapy with established cardiovascular disease (CVD), or at high risk for a CVD event but without established CVD. However, reduction of CV events by bempedoic acid in patients with documented CVD is modest and not statistically significant. The CLEAR Outcomes trial is the largest randomized trial of bempedoic acid including 13,970 patients; 70% of whom had documented CVD (secondary prevention cohort), and 30% were considered high CV risk but without established CV disease (primary prevention cohort). The primary outcome of the CLEAR OUTCOMES trial was a composite of death from CV causes, nonfatal MI, nonfatal stroke, or coronary revascularization (MACE-4). After a median follow-up of 40.6 months, the incidence of CV event was significantly decreased in the bempedoic group versus the placebo group in the whole study population; hazard ratio (HR) 0.87; 95% CI, 0.79 to 0.96; P=0.004). However, this decrease in CV events was mainly driven by the reduction of MACE-4 in the primary prevention cohort; HR 0.68 (95% CI, 0.53 to 0.87), whereas the corresponding reduction in the secondary prevention cohort was more modest; HR 0.91 (95% CI 0.82 to 1.01), Pinteraction=0.03. Results of a post-hoc analysis of the CLEAR Outcomes trial suggested possible increase in all-cause mortality; risk ratio (RR) 1.15 and CV mortality RR 1.21 in the secondary prevention patients. Conversely, in the primary prevention group, there was decrease in all-cause mortality RR 0.70 and CV mortality RR 0.58. While the investigators of the CLEAR Outcomes trial published results of the primary prevention group separately, they did not report those results in the larger secondary group despite greater number of CV events. A randomized trial evaluating bempedoic acid in patients with documented CVD is required to clarify its efficacy and safety in this group of patients. Until such trial is available, the use of bempedoic acid is not recommended for secondary prevention of CV disease.

Keywords: bempedoic acid; cardiovascular effects; mortality; primary prevention; secondary prevention

Introduction

Bempedoic acid deceases cholesterol synthesis by inhibiting ATP-citrate lipase (ACL), and thus works upstream of the enzyme 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase inhibited by statins in the cholesterol synthesis pathway [1]. Decreased production of intra-hepatic cholesterol by bempedoic acid leads to upregulation of hepatic LDL-C receptors and increased clearance of LDL particles from the blood stream and subsequent lowering of circulating LDL-C levels [1]. Bempedoic acid is a prodrug that requires activation by a liver specific enzyme not present in skeletal muscle. This finding may explain the absence of muscle-associated adverse effects with use of bempedoic acid in contrast to statins [1]. The Federal Drug Administration (FDA) has approved bempedoic acid to reduce risk of MI or coronary revascularization in adults with established CVD who are unable to take recommended statin therapy [2]. Moreover, the International Lipid Expert Panel (ILEP) has recommended the use of bempedoic acid in patients with atherosclerotic CVD in combination with statins and other lipid-lowering drugs when the low-density lipoprotein-cholesterol (LDL-C) targets were not met [3]. However, the previous indications by regulatory agencies and international societies may not be based on strong clinical evidence. Such evidence was derived from the results of the largest and longest-term randomized trial of bempedoic acid called the CLEAR Outcomes trial [4]. The latter study showed significant benefit of bempedoic acid in primary prevention but did not show convincing CV benefit of bempedoic acid in secondary prevention [4]. The main purpose of this article is to clarify the effects of bempedoic acid on hard CV endpoints in the primary and secondary prevention settings.

Overview of the CLEAR Outcomes trial

The CLEAR trial is a large (n=13,970) randomized, double-blind, placebo-controlled international study [4]. Patients' mean age was 66 years (range 21-92), 48% were women and 91% were Whites [4]. At study entry, mean body mass index (BMI) was 30.0 kg/m^2, 45% of patients had type 2 diabetes, and mean LDL-C levels were 139 mg/dl [4]. All patients were statin-intolerant defined as being unable or unwilling to receive statins owing to an adverse effect [4]. Meanwhile, 23% of patients were tolerating "very low" dose of statin and still regarded as statin intolerant [4]. At baseline, 70% of patients had documented CVD (secondary-prevention patients) including coronary artery disease (51%), cerebrovascular atherosclerotic diseases (15%), and peripheral vascular diseases (12%) [4]. The remaining 30% of subjects were considered at high risk for CVD (primary-prevention patients) based on at least one of the following criteria: diabetes mellitus in women over 65 years of age or males over 60 years of age, a Reynolds Risk score >30% or a SCORE Risk score >7.5% over 10 years, coronary artery calcium > 400 Agatston units [4]. Patients were assigned to bempedoic acid 180 mg orally once daily (n=6,992) or matched placebo (n=6,978).

Main results of the CLEAR Outcomes trial

The primary outcome was a 4-component composite of death from CV causes, nonfatal MI, nonfatal stroke, or coronary revascularization (MACE-4) as assessed in a time-to-first event analysis [4]. After a median follow-up of 40.6 months, the incidence of a primary end-point event in the whole study population was significantly reduced with bempedoic acid than with placebo, 11.7% vs 13.3%; HR 0.87; 95% CI, 0.76 to 0.96; P=0.006) [4]. However, when the primary prevention and secondary prevention groups of patients were analyzed separately, reduction in MACE-4 was significant only in the primary prevention subgroup; HR 0.68 (95% CI, 0.53 to 0.87) and no longer significant in the larger secondary-prevention group; HR 0.91 (95% CI, 0.82 to 1.01), $P_{interaction}$ = 0.03 [4]. In fact, the only significant interaction in the MACE-4 response to bempedoic acid was related to the baseline CV risk i.e. primary prevention versus secondary prevention status [4]. No significant interaction between the primary outcome and other given subgroup status (e.g. gender, BMI, baseline LDL-C and diabetes status) was demonstrated [4]. This finding was unexpected, particularly that number of CV events was 4.7 to 6.4-fold higher among patients with established CVD compared with those with only CV risk factors [4]. It should be emphasized that baseline values as well as and reductions in levels of LDL-C and C-reactive protein (CRP) by bempedoic acid were approximately the same in the primary and secondary prevention cohorts [4-5]. Therefore, differences in such levels between the primary and secondary cohorts could not explain the difference in outcomes. Compared to placebo, percentage reduction in LDL-C levels after 6 months and CRP were 21.1% (95% CI, 20.3 to 21.9) and 21.6% (95% CI, 19.6 to 2.37), respectively [4].

Effects of bempedoic acid on mortality

Sayed and Brophy [5] performed a post-hoc analysis of the overall and primary prevention reports of CLEAR-Outcomes trial to reconstruct data for the secondary prevention patients. These authors found that all-cause mortality was decreased by bempedoic acid in the primary prevention population by 30% (risk ratio 0.70; 95% credible interval 0.51 to 0.92) [5]. Conversely, in the secondary prevention cohort, there was trend towards increasing all-cause mortality by 15% (RR 1.15; 95% credible interval 0.99 to 1.33) [5]. Similar pattern was observed with respected to CV mortality, with a risk reduction of 42% in the primary prevention setting (RR 0.52, 95% credible interval 0.38 to 0.86) and 21% increased risk in the secondary prevention cohort (RR 1.21; 95% credible interval 1.00 to 1.45) [5]. Certainly, these mortality data in the secondary prevention cohort are disturbing and requires confirmation by further studies.

Separate analysis of the primary prevention cohort of the CLEAR Outcomes trial

The CLEAR Outcomes investigators conducted separate analysis of the primary prevention subgroup of patients (n=4,206) [6]. After a median follow-up of 39.9 months, the reduction in the primary outcome MACE-4 was statistically significant and was very close to that reported in the original trial with a HR of 0.70 (95% CI, 0.55 to 0.89; P=0.002) [4,6]. Furthermore, while no significant effects of bempedoic acid on mortality was shown in the whole CLEAR-Outcomes trial, in the primary prevention cohort, there were reductions in all-cause mortality (HR 0.73; 95% CI 0.54 to 0.88) and CV mortality (HR 0.61; 95% CI, 0.41 to 0.92) [6]. The report of the results of primary prevention data separately while not reporting corresponding data in the larger secondary prevention cohort raises an important question and concern. The most likely answer is that the Clear Outcomes investigators reported the more favorable results of bempedoic acid in the primary prevention cohort and did not like to reveal the less favorable, and possibly harmful results in the secondary prevention cohort [5].

Explanations of the discrepant effects of bempedoic acid in primary versus secondary prevention

There are several possible explanations for the less favorable CV effects of bempedoic acid in the secondary prevention patients. First, it may reflect a play of chance [7]. Second, as Alexander hypothesized, more benefit of bempedoic acid might be achieved in early stages of CVD [7]. Third, the more extensive use of CV protective drugs in the secondary prevention group potentially blunting any further benefit by bempedoic acid. Fourth, while patients' characteristics of the secondary prevention cohort were not reported separately, there were some differences observed between characteristics of subjects included in the primary cohort versus the whole study population [4,6]. For instance, proportions of women and patients with diabetes were higher in the primary prevention cohort versus the whole patient population; 59% and 66% versus 48% and 45% [4,6]. However, as mentioned earlier, response to bempedoic acid did not change significantly by gender or diabetes status [4]. Therefore, to clarify the role of bempedoic acid in secondary prevention of CVD, a dedicated randomized trial should be conducted in patients with established CVD.

Conclusions and clinical implications

Subgroup analysis of the CLEAR Outcomes trial suggested a heterogeneity of bempodeic acid effect on CV events with substantial CV benefits in the primary prevention setting, but much less pronounced effects in the secondary prevention setting [4]. Moreover, subgroup analysis suggested a possible increase in overall and CV mortality in association with bempedoic acid in the secondary prevention patients [5]. However, results derived from subgroup analysis may be prone for multiple statistical limitations and should not be regarded as conclusive [8]. Therefore, to clarify the role of bempedoic acid in secondary prevention of CVD, a dedicated randomized trial should be conducted in patients with established CVD. In the meantime, the investigators of the CLEAR Outcomes trial should publish a separate analysis of the results in the secondary prevention cohort as they did regarding the primary prevention patients [6]. Based on available data, bempedoic acid may be used in patients with high CV risk and LDL-C levels above targets to decrease CV events and mortality (i.e in primary prevention of CVD). However, until more data becomes available, bempedoic acid should not be used in patients with established CVD due to possible increase in CV and all-cause mortality and its modest efficacy in decreasing CV events.

Conflict of interest

The author does not any conflict to declare.

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