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Key publications

**Bempedoic acid; a new LDL-c lowering drug**

Statins remain the preferred choice of treatment for lowering LDL-c; however additional pharmacological strategies to reduce LDL-c are needed for those unable to tolerate statins as add on therapy if LDL-c remains elevated. Innovative strategies developed, e.g.,
cholesterol absorption inhibitors and PCSK9, are incorporated in our current pharmacological armamentarium. Bempedoic acid is one of the more recent drugs now available. It is an oral drug that, similar to statins, inhibits cholesterol synthesis by targeting ATP citrate lyase (ACL). Notably, the pro-drug activation can only occur in the liver, suggesting that muscle side-effects are unlikely. This article reviews the pharmacological properties, mechanism of action, completed phase I-III trials, and meta-analyses of the bempedoic acid studies. This new drug seems to be well tolerated with a good safety profile and modest LDL-c lowering properties both as mono-therapy (± 20% LDL-c reduction) and combined with ezetimibe (± 38% LDL-c reduction) and statins. In the US, the FDA approved both Nexletol (bempedoic acid 180 mg Significant reductions with triple therapy vs. placebo were also observed for non–high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein (p < 0.001 for all). With triple-therapy, 90% of patients achieved LDL-C <70 mg/dL and 95% of patients had ≥50% lower LDL-C from baseline to week 6; predicted around USD 10,=/day for mono-therapy (USD 3 600/year; compared to PCSK9ab USD 4 500/year); the CLEAR Outcomes study will provide the CV outcome data for this drug and will be completed in the second half of 2022.


Bempedoic acid + ezetimibe + atorvastatin results in >60% LDL-c reduction

In this phase II double-blind randomized placebo-controlled study, a triple therapy consisting of bempedoic acid 180 mg + ezetimibe 10 mg and atorvastatin 20 mg (N=43) was compared to placebo (N=20). The 63 participants had a mean age of 61.2 years and a baseline LDL-c of 154.8 mg. After 6 weeks, the patients allocated to triple therapy reduced their LDL-c by -63.6% vs. -3.1% in the placebo group. A significant difference of -60.5% (-68.0% to -53.0%; p < 0.001). Non–high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein were significantly reduced as well (p < 0.001 for all). Approximately 90% of the patients using triple-therapy achieved LDL-C <70 mg/dL, and 95% had ≥50% lower LDL-C. The reported treatment-associated side-effects were mild to moderate and significant increases in both transaminases and CPK were absent. The authors concluded that triple therapy with bempedoic acid 180 mg, ezetimibe 10 mg, and atorvastatin 20 mg was safe and well-tolerated. Significant reductions of LDL-c, non–HDL-c, total-c, apolipoprotein B, and high sensitivity C-reactive protein (p < 0.001 for all) were observed; this allowed 90% of the patients to achieve an LDL-C <70 mg/dL and 95% of the patients had ≥50% LDL-C after 6 weeks of therapy.

Rubino J, MacDougall DE, Sterling LR et al. Combination of bempedoic acid, ezetimibe, and

Meta-analysis of lipid-lowering drugs in HTG patients

Elevated triglycerides are a common occurrence in patients and associated with increased ASCVD risk. This meta-analysis explored the CV benefits of commonly used lipid-lowering drugs, statins, niacin, fibrates, omega-3 fatty acids, and ezetimibe. Articles were selected from inception to July 6, 2020, from PubMed, EMBASE, and Cochrane libraries. Of the 2005 articles, 21 trials were selected for the final analysis (N=56 471). Of note, the included trials differed significantly in the patient’s characteristics. In the non-statin intervention studies, statin use was either not restricted or actively used in both study arms. Overall, simvastatin showed superior outcomes in reducing MACE risk in patients with elevated TG’s; OR: 2.38 (1.55–3.66). EPA, but not omega-3 fatty acids, was effective (OR: 1.32; 1.19–1.46), as was gemfibrozil among the fibrates OR: 1.32 (1.19–1.46). In the hypertriglyceridemic patients (TG > 200 mg/dL) MACE reductions were noted for bezafibrate, OR: 0.56 (0.33–0.94); EPA, OR: 0.72 (0.62–0.82), and pravastatin, OR: 1.33 (1.01–1.75) significantly reduced the MACE risk.

Statins in thrombolysed stroke patients – A 5-year follow-up study

The effects of statins in thrombolysed stroke patients were evaluated in this single-center study. From October 2008, 542 consecutive stroke patients treated with rt-PA were followed for 5-years. The primary endpoint was mortality (assessed in hospital and 3-months after discharge). The secondary outcome was intracerebral haemorrhage. Statins were used at hospital admission in 138 patients (25.5%); statins were initiated in 190 patients (35.1%), and 193 (35.6%) never received statins. Those that were pre-treated with statins were older and more frequently had previous illnesses (arterial hypertension, diabetes mellitus, and previous cerebral infarctions). The National Institutes of Health Stroke Scale (NIHSS) scores were similar, 11 vs. 11 (P=0.76). Mortality observed after 3-months was similar in pre-statin users and patients that started taking statin during their hospital stay, 7.6% vs. 8%; (P = 0.9). In-hospital mortality was reduced in statin users compared to no-statin use, 6.6% vs. 17.0 (P = 0.005). This was also observed after 3-months; 10.7% vs. 23.7% (P = 0.005) of the patients died respectively. Intriguingly this was also the case for patients that initiated statins during their hospital stay compared to patients who did not receive statins; 3-month mortality: 7.1% vs. 23.7% (P < 0.001). The majority of patients discharged (60%) had good functional outcome (mRS ≤ 2), the majority used statins; 69.6% (P < 0.001) of those continued using
statins after discharge. An important finding in this study was that symptomatic intracerebral hemorrhages, diagnosed by CT scan at hospital admission, were not different in those pre-treated with statins compared to those not using statins; 8.8% vs. 8.7% (P = 0.96). Overall, these findings support the use of statins in patients at risk for ischemic strokes; it is reassuring to note that statin use was not associated with an increased risk for cerebral haemorrhage’s.


Statins in putative FH patients – 4S study re-analysis

Individuals diagnosed with Familial Hypercholesterolemia (FH) are categorized as very-high ASCVD risk patients. Trial evidence for FH patients is scarce due to the lack of clinical outcome trials designed to evaluate patients’ particular group. In this re-analysis of the 4S study, clinical endpoints in the patients with an LDL-c <4.9 were compared with those with an LDL-c >4.9 mmol/L. The latter group was subsequently stratified into four categories (based on Dutch Lipid Clinic Network Criteria – DLCN); the presence of none, one or both of “premature CAD” and “family history of CAD”. Participants were defined as having an FH phenotype. Of the 4431 participants, 2267 and 2164 participants had LDL-C <4.9 and ≥ 4.9 mmol/L, respectively. Both groups showed significant benefits of mortality endpoints and major coronary events (MCE) over 5.4 years Patients categorized as FH (N=152) derived greater absolute risk reductions (ARR); 4.1–4.3% for mortality endpoints, versus 2.5–2.8%. No difference was noted in LDL-c reductions when FH patients were compared to the three categories of non-FH patients with LDL-c >4.9 mmol/l. FH patients derived greater benefit from similar LDL-c reductions; all-cause death: 84% relative risk reduction (p = 0.046); MACE: 55% reduction (p = 0.0297). the absolute risk reduction (ARR) was superior in FH patients; ARR for all-cause mortality: 6.6% and for MACE 13.2%; versus 3.8% and 8.3%, respectively. The authors concluded that FH patients with an FH phenotype were shown to derive greater clinical benefits from similar LDL-c reductions in patients that were comparable but lacked the FH phenotype.

Relevant publications


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