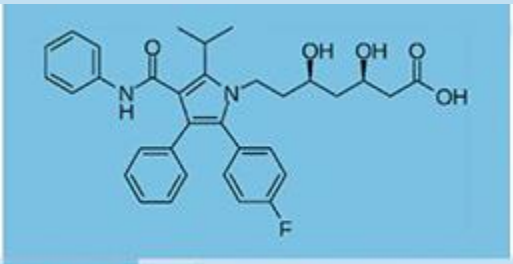
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 04, 2021

Curated by Peter Lansberg,
a Dutch lipidologist and educator, and
reviewed by prof. Philip Barter, Past President of the
International Atherosclerosis Society.

The IAS statin literature update will keep you up-to-date with all recent statin publications, using a curated approach to select relevant articles.

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.

Susekov AV, Korol LA, Watts GF. **Bempedoic Acid in the Treatment of Patients with Dyslipidemias and Statin Intolerance.** Cardiovasc Drugs Ther 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33502687

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**

atorvastatin in patients with hypercholesterolemia: A randomized clinical trial. Atherosclerosis 2020. http://www.ncbi.nlm.nih.gov/pubmed/?term=33514449

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. Qi YY, Yan L, Wang ZM *et al.* Comparative efficacy of pharmacological agents on reducing the risk of major adverse cardiovascular events in the hypertriglyceridemia population: a network meta-analysis. Diabetology & metabolic syndrome 2021; 13:15. http://www.ncbi.nlm.nih.gov/pubmed/?term=33514420

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.

Bruning T, Al-Khaled M. **Do statins reduce the mortality rate in stroke patients treated with systemic thrombolysis in a 5-year.** Neural regeneration research 2021; 16:1807-1812. http://www.ncbi.nlm.nih.gov/pubmed/?term=33510087

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.

Vallejo-Vaz AJ, Packard CJ, Ference BA *et al.* **LDL-cholesterol lowering and clinical outcomes in hypercholesterolemic subjects with and without a familial hypercholesterolemia phenotype: Analysis from the secondary prevention 4S trial.** Atherosclerosis 2021; 320:1-9. http://www.ncbi.nlm.nih.gov/pubmed/?term=33497862

Relevant publications

1. Uematsu M, Nakamura T, Horikoshi T *et al.* Echolucency of carotid plaque is useful for selecting high-risk patients with chronic coronary artery disease who benefit from intensive lipid-lowering therapy. J Cardiol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33500186
2. Silva-Almodóvar A, Hackim E, Wolk H, Nahata MC. Potentially Inappropriately Prescribed Medications Among Medicare Medication Therapy Management Eligible Patients with Chronic Kidney Disease: an Observational Analysis. Journal of general internal medicine 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33506400
3. Nicolau JC, Furtado RHM, Dalçóquio TF *et al.* Factors associated with actively working in the very long-term following acute coronary syndrome. Clinics (Sao Paulo, Brazil) 2021; 76:e2553. http://www.ncbi.nlm.nih.gov/pubmed/?term=33503196
4. Lin CK, Chen PY, Wu YY *et al.* Adjunctive Statin Therapy Reduces Mortality After Acute Hemorrhagic Stroke. Risk Manag Healthc Policy 2021; 14:177-183. http://www.ncbi.nlm.nih.gov/pubmed/?term=33488130
5. Majd Z, Mohan A, Paranjpe R, Abughosh SM. Identifying adherent patients to newly initiated statins using previous adherence to chronic medications. Journal of managed care & specialty pharmacy 2021; 27:186-197. http://www.ncbi.nlm.nih.gov/pubmed/?term=33506725
6. Khan MS, Ishaq M, Ayub MT *et al.* The Novelty of Icosapent Ethyl in the Management of Hypertriglyceridemia and Alleviating Cardiovascular Risk. Journal of lipids 2021; 2021:6696915. http://www.ncbi.nlm.nih.gov/pubmed/?term=33505729
7. Keni R, Sekhar A, Gourishetti K *et al.* Role of Statins in New-onset Diabetes Mellitus: The Underlying Cause, Mechanisms Involved, and Strategies to Combat. Current drug targets 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33494673
8. Chen CY, Wu WT, Wang YL, Liao KM. Statins for the Treatment of Pulmonary Hypertension in Patients with Chronic Obstructive Pulmonary Disease. Frontiers in pharmacology 2020; 11:613761. http://www.ncbi.nlm.nih.gov/pubmed/?term=33510638
9. Ambrosy AP, Malik UI, Thomas RC *et al.* Rationale and Design of the Pragmatic Randomized Trial of Icosapent Ethyl for High Cardiovascular Risk Adults (MITIGATE). Am Heart J 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33516752
10. Zhang MM, Bahal R, Rasmussen TP *et al.* The growth of siRNA-based therapeutics: Updated clinical studies. Biochem Pharmacol 2021:114432. http://www.ncbi.nlm.nih.gov/pubmed/?term=33513339

11. Yun HJ, Ding Y. How to remove those bloody collections: Nonsurgical treatment options for chronic subdural hematoma. Brain circulation 2020; 6:254-259. http://www.ncbi.nlm.nih.gov/pubmed/?term=33506148
12. Russo GI, Larganà G, Sebastianelli A *et al.* The Investigative Role of Statins in Ameliorating Lower Urinary Tract Symptoms (LUTS): A Systematic Review. Journal of clinical medicine 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=33499215
13. Roan JN, Lin WH, Tsai MT *et al.* Rosuvastatin Failed to Improve Arteriovenous Fistula Patency for Hemodialysis in Diabetic Patients - A Randomized Clinical Trial. Acta Cardiologica Sinica 2021; 37:18-29. http://www.ncbi.nlm.nih.gov/pubmed/?term=33488024
14. Mollazadeh H, Tavana E, Fanni G *et al.* Effects of statins on mitochondrial pathways. Journal of cachexia, sarcopenia and muscle 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33511728
15. Lempel M, Molla E. Treatment of Statin-Induced Necrotizing Autoimmune Myopathy With Glucocorticoid Monotherapy. Cureus 2020; 12:e12086. http://www.ncbi.nlm.nih.gov/pubmed/?term=33489504
16. Kaiser H, Kvist-Hansen A, Krakauer M *et al.* Statin Therapy and Vascular Inflammation Detected by Positron Emission Tomography/Computed Tomography in Patients with Psoriasis. Acta Derm Venereol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33491097
17. Jenkins DJA, Spence JD, Giovannucci EL *et al.* Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment: JACC Focus Seminar. J Am Coll Cardiol 2021; 77:423-436. http://www.ncbi.nlm.nih.gov/pubmed/?term=33509399
18. Huynh LM, Keit E, Schuller AA *et al.* Impact of statin use on overall and time to biochemical failure following radical prostatectomy or radiation therapy. World J Urol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33502557
19. Futema M, Ramaswami U, Tichy L *et al.* Comparison of the mutation spectrum and association with pre and post treatment lipid measures of children with heterozygous familial hypercholesterolaemia (FH) from eight European countries. Atherosclerosis 2021; 319:108-117. http://www.ncbi.nlm.nih.gov/pubmed/?term=33508743
20. Billinger SA, Whitaker AA, Morton A *et al.* Pilot Study to Characterize Middle Cerebral Artery Dynamic Response to an Acute Bout of Moderate Intensity Exercise at 3- and 6-Months Poststroke. J Am Heart Assoc 2021; 10:e017821. http://www.ncbi.nlm.nih.gov/pubmed/?term=33496192

Basic Science publications

1. Wu YR, Li L, Sun XC *et al.* Diallyl disulfide improves lipid metabolism by inhibiting PCSK9 expression and increasing LDL uptake via PI3K/Akt-SREBP2 pathway in HepG2 cells. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021; 31:322-332. http://www.ncbi.nlm.nih.gov/pubmed/?term=33500108
2. Natalia ML, Patricia GL. Statins as adjuvants in the treatment of ovarian cancer: Controversy and misunderstanding. Eur J Pharmacol 2021; 896:173915. http://www.ncbi.nlm.nih.gov/pubmed/?term=33513335
3. Liu W, Wang M, Shen L *et al.* SHP2-mediated mitophagy boosted by lovastatin in neuronal cells alleviates parkinsonism in mice. Signal Transduct Target Ther 2021; 6:34. http://www.ncbi.nlm.nih.gov/pubmed/?term=33514686
4. Liu Q, Xu J, Liao K, Tang N. Oral Bioavailability Improvement of Tailored Rosuvastatin Loaded Niosomal Nanocarriers to Manage Ischemic Heart Disease: Optimization, Ex Vivo and In Vivo Studies. AAPS PharmSciTech 2021; 22:58. http://www.ncbi.nlm.nih.gov/pubmed/?term=33502651
5. Lian Z, Song JX, Yu SR *et al.* Therapeutic targets of rosuvastatin on heart failure and associated biological mechanisms: A study of network pharmacology and experimental validation. Eur J Pharmacol 2021; 895:173888. http://www.ncbi.nlm.nih.gov/pubmed/?term=33493484
6. Christiansen LB, Dohlmann TL, Ludvigsen TP *et al.* Atorvastatin impairs liver mitochondrial function in obese Göttingen Minipigs but heart and skeletal muscle are not affected. Scientific reports 2021; 11:2167. http://www.ncbi.nlm.nih.gov/pubmed/?term=33500513
7. Bergeron S, Barus R, Leboullenger C *et al.* Beneficial effects of atorvastatin on sex-specific cognitive impairment induced by a cerebral microhaemorrhage in a murine model. Br J Pharmacol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33502755
8. Arafa MF, Alshaikh RA, Abdelquader MM, El Maghraby GM. Co-processing of Atorvastatin and Ezetimibe for Enhanced Dissolution Rate: In Vitro and In Vivo Correlation. AAPS PharmSciTech 2021; 22:59. http://www.ncbi.nlm.nih.gov/pubmed/?term=33517486
9. Salem HF, Kharshoum RM, Abou-Taleb HA *et al.* Fabrication and Appraisal of Simvastatin via Tailored Niosomal Nanovesicles for Transdermal Delivery

Enhancement: In Vitro and In Vivo Assessment. Pharmaceutics 2021; 13. http://www.ncbi.nlm.nih.gov/pubmed/?term=33494472

10. Ryngajłło M, Boruta T, Bizukojć M. Complete genome sequence of lovastatin producer Aspergillus terreus ATCC 20542 and evaluation of genomic diversity among A. terreus strains. Applied microbiology and biotechnology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33515286
11. Majeed ML, Ghafil FA, Fatima G *et al.* Anti-Atherosclerotic and Anti-Inflammatory Effects of Curcumin on Hypercholesterolemic Male Rabbits. Indian J Clin Biochem 2021; 36:74-80. http://www.ncbi.nlm.nih.gov/pubmed/?term=33505130

This activity is supported by an educational grant from Viatris.
© P.J. Lansberg