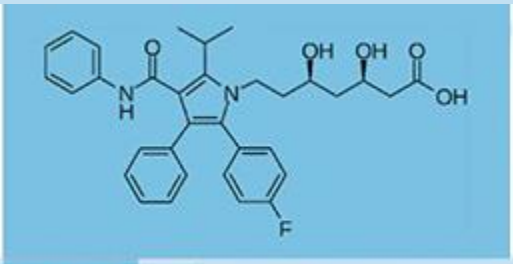
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 11, 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

Shift in targets: from LDL- to Apo B (Non-HDL-c)

Current guidelines focus on LDL-c as the primary target. However, based on accumulating data from large registries and clinical trials, more accurate markers such as apo B and Non-HDL-care suggested to improve accuracy. In this analysis of the Copenhagen General Population Study 13 015 statin users, with a median follow-up time of 8 years, apo B, Non-HDL-c, and LDL-c were compared for their prowess to predict mortality and myocardial infarction (MI) risk. Patients with increased apo B, above the median, to patients with LDL-c below the median resulted in an HR: 1.21 (1.07-1.31) for all-cause mortality and an HR: 1.49 (1.15-1.92) for MI. Performing a similar calculation for non-HDL-c and LDL-c resulted in HR's of 1.18 (1.02-1.36) and 1.78 (1.35 -2.34), respectively. This contrasted with discordant LDL-c compared to low apo B and low Non-HDL-c, which was not associated with increase MI or mortality risk. Comparing discordant high apo B with low Non-HDL-c resulted in an increased risk for total mortality and MI; HR: 1.21 (1.03-1.41) and HR: 0.93 (0.62-1.40). A higher than the median plasma concentration of apo B + Non-HDL-c compared to a below-median value of LDL-c resulted in an HR:1.23 (1.07-1.43) for all-cause mortality and an HR: 1.82 (1.37-2.42) for MI. Based on these findings, the authors concluded that both Apo B and Non-HDL-c, not LDL-c, are associated with residual risk for all-cause mortality and MI in statin-treated patients. Discordance analysis showed that apo B is a more accurate marker for all-cause mortality when compared to LDL-c and Non-HDL-c. This was also observed for MI when compared to LDL-c.
Johannesen CDL, Mortensen MB, Langsted A, Nordestgaard BG. Apolipoprotein B and Non-

HDL Cholesterol Better Reflect Residual Risk Than LDL Cholesterol in Statin-Treated Patients. J Am Coll Cardiol 2021; 77:1439-1450.
Stone NJ, Lloyd-Jones D. **Tracking Residual Risk: Time for a Change?** J Am Coll Cardiol 2021; 77:1451-1453. http://www.ncbi.nlm.nih.gov/pubmed/?term=33736828

Comparing LDL-c lowering effects of different statin in FH patients

Optimal LDL-c management in familial hypercholesterolemia (FH) patients requires the use of high-dose potent statins as well as the combination of statins with ezetimibe or PCSK9ab. The Spanish Arteriosclerosis Society Registry was queried for probable/definite FH patients. Data drug therapy and lipid profile were available for 2894 patients. Patients with confirmed genetic mutation showed better LDL-c reductions when compared to definite FH patients that lacked a genetic mutation. Suboptimal response to statins (<15% or <30% LDL-c reduction) was noted in 13.5% of FH patients with a mutation compared to 20.3% definite FH patients but without a mutation. The reduction of LDL-c ranged from 30.2 ±17.0% in patients treated with simvastatin 10 mg to 48.2 ±17.0% in patients that received rosuvastatin 40 mg. Adding ezetimibe to rosuvastatin 5, 10, 20, and 40 mg resulted in an additional LDL-c reduction of 26, 24, 21, and 24%, respectively. When statins were ranked for their potency to reduce LDL-c, rosuvastatin was the most potent, followed by atorvastatin and simvastatin. However, maximum dosages of atorvastatin and rosuvastatin were nearly equivalent. The authors noted that approximately 1 in 5 FH patients had s suboptimal response on high-dose, high-intensity statins.
Climent E, Marco-Benedí V, Benaiges D *et al.* **Impact of statin therapy on LDL and non-HDL cholesterol levels in subjects with heterozygous familial hypercholesterolaemia.** Nutrition, metabolism, and cardiovascular diseases : NMCD 2021.
http://www.ncbi.nlm.nih.gov/pubmed/?term=33744038

Antecedent statin use associated with improved mortality in hospitalized COVID-19 patients

In the quest for repurposing existing drugs for improving outcomes in COVID-19 patients, statins are likely to provide benefits. In this retrospective study of 1014 patients from a single academic US hospital and with confirmed PCR diagnosis, patients with antecedent use of statins (N= 454) were compared to those that were not using statins before admission (N= 560). Based on a multivariate regression model, statin use was associated with a reduced total mortality compared to no statins; OR: 0.66 (0.64-0.95; p=0.03). Using a propensity score-matched analysis, comparing 233 statin users with 233 patients not prescribed statin prior to hospital admission, a significant reduction of total mortality was observed as well; OR:0.56 (0.37-0.83; p=0.004). Statin use was associated with significantly improved survival of patients with COVID-19. These observational findings warrant the pursuit of randomized controlled trials to confirm these findings.
Lohia P, Kapur S, Benjaram S, Mir T. **Association between antecedent statin use and severe disease outcomes in COVID-19: A retrospective study with propensity score matching**. J Clin Lipidol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33726984

Managing LDL-c in FH patients; a 10-year follow-up study

The increased risk of premature ASCVD events is well documented, with new and potent add-on LDL-c leering drugs such as PCSK9ab achieving guideline-recommended targets are becoming realistic. The effects of intensive lipid management were evaluated in the Treat To Target FH (TTTFH) study. Included were 357 adults with mean total cholesterol of 9.8 mmol/L; 279 patients came for a follow-up visit after a median period of 10-years. A pathogenic mutation was present in 86.4% of the participants; the remaining13.6% were clinically diagnosed. LDL-c was reduced to 3.0 (2.9-3.9) mmol/L. High-intensity statins were used by 85.2% of the men and 60.8% of the women. Mean LDL-c was higher in women 3.3 mmol/l compared to men 2.8 mmol/L P=0.004). Patients that used PCSK9ab (N=25) were able to achieve a mean LDL-c of 2.0 mmol/L. At study entry, 57 patients (20.4%) were diagnosed with ASCVD, and a recurrence was observed in 46 patients (80.4%). In the 222 primary prevention patients (79.8%), 29 (13.1%) develop a first-time ASCVD event during the study. FH patients managed at a specialized lipid clinic and treated intensively were able to

achieve a mean LDL-c of 3.0 mmol/L, and only a few patients were using PCSK9ab. Those with manifest ASCVD at the study start had a very high risk for recurrences (80.7%) during the 10-year follow-up; this contrasted with the limited ASCVD risk observed in FH patient free CVD complications (13%).
Arnesen KE, Phung AV, Randsborg K *et al.* **Risk of Recurrent Coronary Events in Patients With Familial Hypercholesterolemia; A 10-Years Prospective Study**. Frontiers in pharmacology 2020; 11:560958. http://www.ncbi.nlm.nih.gov/pubmed/?term=33737874

Systematic review of statin use in cirrhotic patients

This systematic review evaluated the safety and efficacy of statin use in patients with cirrhosis. Using the common bibliography resources, 22 articles and two drug monographs. The authors set out to address pharmacokinetics (PK), safety, and CV outcomes in cirrhotic patients that use a statin. For patients with Child-Pugh class A cirrhosis, only minimal PK changes were observed in patients that used rosuvastatin and pitavastatin. Pronounced PK changes were noted for atorvastatin. No studies with simvastatin addressed PK changes, although this was the most frequently used statin. It was not possible to establish effects on CV outcomes due to a lack of data. Only simvastatin, atorvastatin, and pravastatin were used in clinical studies. Rhabdomyolysis frequency was 2% in patients that used simvastatin 40 mg, a 40-fold increase compared to rhabdomyolysis reports in non-cirrhotic patients. For patients that used simvastatin 20 mg, atorvastatin 20 mg, or pravastatin, no rhabdomyolysis was reported. No over liver failure and no Drug-induced liver injury (DILI) were reported. Based on these limited reports, the authors recommended refraining from using simvastatin 40 mg in patients with advanced cirrhosis. Insufficient safety data was available for simvastatin 20 mg and the other statins. The lack of data, and evidence on dose adjustments, does not support the use of statins to reduce CV risk or improve hepatic outcomes in patients with advanced cirrhosis.
Sung S, Al-Karaghouli M, Kalainy S *et al.* **A systematic review on pharmacokinetics, cardiovascular outcomes and safety profiles of statins in cirrhosis**. BMC gastroenterology 2021; 21:120. http://www.ncbi.nlm.nih.gov/pubmed/?term=33726685

Relevant publications

1. Wang Y, Li Q, Yuan Z *et al.* Statin Use and Benefits of Thyroid Function: A Retrospective Cohort Study. Frontiers in endocrinology 2021; 12:578909. http://www.ncbi.nlm.nih.gov/pubmed/?term=33737906
2. Tian Y, Wang J, Liu Y *et al.* MassARRAY multigene screening combined with LDL-C and sdLDL-C detection for more favorable outcomes in type 2 diabetes mellitus therapy. BMC medical genomics 2021; 14:83. http://www.ncbi.nlm.nih.gov/pubmed/?term=33731122
3. Strandberg TE, Kivimäki M. Increased mortality risk associated with statins in the CORONADO study. Diabetes Metab 2021:101250. http://www.ncbi.nlm.nih.gov/pubmed/?term=33744398

4. Lee J, Egolum U, Parihar H *et al.* Effect of Ezetimibe Added to High-Intensity Statin Therapy on Low-Density Lipoprotein Cholesterol Levels: A Meta-Analysis. Cardiology research 2021; 12:98-108. http://www.ncbi.nlm.nih.gov/pubmed/?term=33738013
5. Rosenson RS. Existing and emerging therapies for the treatment of familial hypercholesterolemia. Journal of lipid research 2021:100060. http://www.ncbi.nlm.nih.gov/pubmed/?term=33716107
6. Oh M, Kim H, Shin EW *et al.* Statin/ezetimibe combination therapy vs statin monotherapy for carotid atherosclerotic plaque inflammation. Medicine (Baltimore) 2021; 100:e25114. http://www.ncbi.nlm.nih.gov/pubmed/?term=33725908
7. Masson W, Lobo M, Masson G *et al.* Statin use in patients with elevated serum hepatic transaminases at baseline: A meta-analysis. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33715945
8. Li Y, Guo Y, Zhou M *et al.* Paradoxical effect of statin medication on depressive disorder in first-ever ischemic stroke patients: possible antidepressant-like effect prestroke and the opposite in continuous medication poststroke. International clinical psychopharmacology 2021; 36:147-153. http://www.ncbi.nlm.nih.gov/pubmed/?term=33724252
9. Ip YMB, Au L, Chan YYA *et al.* EXPRESS: Evolving Ischemic Stroke Subtypes in 15 years: A hospital-based observational study. Int J Stroke 2021:17474930211005953. http://www.ncbi.nlm.nih.gov/pubmed/?term=33724087
10. Huang YJ, Kao S, Kao LT *et al.* Association Between Statin Use and Exacerbation of Chronic Obstructive Pulmonary Disease Among Patients Receiving Corticosteroids. International journal of chronic obstructive pulmonary disease 2021; 16:591-602. http://www.ncbi.nlm.nih.gov/pubmed/?term=33716501
11. Ciardullo S, Perseghin G. Statin use is associated with lower prevalence of advanced liver fibrosis in patients with type 2 diabetes. Metabolism 2021:154752. http://www.ncbi.nlm.nih.gov/pubmed/?term=33716004
12. Farooque U, Lohano AK, Dahri Q *et al.* The Pattern of Dyslipidemia in Chronic Liver Disease Patients. Cureus 2021; 13:e13259. http://www.ncbi.nlm.nih.gov/pubmed/?term=33728198
13. Cho HW, Song IA, Oh TK. Prior Statin Therapy and Mortality After Extracorporeal Membrane Oxygenation Therapy: A Retrospective, Population-Based, Cohort Study. Journal of cardiothoracic and vascular anesthesia 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33715948
14. Brodney S, Valentine KD, Sepucha K *et al.* Patient Preference Distribution for Use of Statin Therapy. JAMA network open 2021; 4:e210661. http://www.ncbi.nlm.nih.gov/pubmed/?term=33720368

15. Schulz M, Czwikla J, Schmidt A *et al.* [Medical specialist undertreatment in nursing home residents-Prevalence and extrapolation]. Zeitschrift fur Gerontologie und Geriatrie 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33725195
16. Šatný M. Fixed-dose combination of rosuvastatin and ezetimibe. Vnitr Lek 2020; 66:513-517. http://www.ncbi.nlm.nih.gov/pubmed/?term=33740852
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18. Phoon IKY, Koh YLE, Guo X *et al.* Compatibility between an overnight fasting and random cholesterol tests in Asians. Scientific reports 2021; 11:6478. http://www.ncbi.nlm.nih.gov/pubmed/?term=33742059
19. Özdener-Poyraz AE, Vaidean G. Preventive Cardiovascular Care in Patients With HIV Infection in an Outpatient Clinic. Journal of pharmacy practice 2021:8971900211000700. http://www.ncbi.nlm.nih.gov/pubmed/?term=33736523
20. Ouahoud S, Jacobs RJ, Peppelenbosch MP *et al.* Kinome-wide analysis of the effect of statins in colorectal cancer. Br J Cancer 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33742146
21. Moorman AJ, Dean LS, Yang E, Drezner JA. Cardiovascular Risk Assessment in the Older Athlete. Sports Health 2021:19417381211004877. http://www.ncbi.nlm.nih.gov/pubmed/?term=33733939
22. Mamidi R, Devineni D, Sun D *et al.* Rosuvastatin Myotoxicity After Starting Canagliflozin Treatment. Annals of internal medicine 2021; 174:431-432. http://www.ncbi.nlm.nih.gov/pubmed/?term=33721528
23. Lecumberri E, Ruiz-Carmona C, Mateos E *et al.* Prognostic Value of Inflammatory Biomarkers in 5-Year Survival After Endovascular Repair of Abdominal Aortic Aneurysms in a Predominantly Male Cohort: Implications for Practice. World journal of surgery 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33721070
24. Brailovski E, Kim RB, Juurlink D. Rosuvastatin Myotoxicity After Starting Canagliflozin Treatment. Annals of internal medicine 2021; 174:432. http://www.ncbi.nlm.nih.gov/pubmed/?term=33721527
25. Bornfeldt KE. Triglyceride lowering by omega-3 fatty acids: a mechanism mediated by N-acyl taurines. J Clin Invest 2021; 131. http://www.ncbi.nlm.nih.gov/pubmed/?term=33720044
26. Alamer A, Te C, Fazel MT. Rosuvastatin Myotoxicity After Starting Canagliflozin Treatment. Annals of internal medicine 2021; 174:431. http://www.ncbi.nlm.nih.gov/pubmed/?term=33721529

Basic Science publications

1. Jia W, Bai T, Zeng J *et al.* Combined Administration of Metformin and Atorvastatin Attenuates Diabetic Cardiomyopathy by Inhibiting Inflammation, Apoptosis, and Oxidative Stress in Type 2 Diabetic Mice. Front Cell Dev Biol 2021; 9:634900. http://www.ncbi.nlm.nih.gov/pubmed/?term=33718370
2. Zhong S, Li L, Liang N *et al.* Acetaldehyde Dehydrogenase 2 regulates HMG-CoA reductase stability and cholesterol synthesis in the liver. Redox biology 2021; 41:101919. http://www.ncbi.nlm.nih.gov/pubmed/?term=33740503
3. van Gemert Y, Kozijn AE, Pouwer MG *et al.* Novel high-intensive cholesterol-lowering therapies do not ameliorate knee OA development in humanized dyslipidemic mice. Osteoarthritis and cartilage 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33722697
4. Kessinger CW, Qi G, Hassan MZO *et al.* Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Imaging Predicts Vein Wall Scarring and Statin Benefit in Murine Venous Thrombosis. Circulation. Cardiovascular imaging 2021:Circimaging120011898. http://www.ncbi.nlm.nih.gov/pubmed/?term=33724049
5. Ikonomopoulou MP, Lopez-Mancheño Y, Novelle MG *et al.* LXR stimulates a metabolic switch and reveals cholesterol homeostasis as a statin target in Tasmanian devil facial tumor disease. Cell Rep 2021; 34:108851. http://www.ncbi.nlm.nih.gov/pubmed/?term=33730574
6. Huber D, Wikén C, Henriksson R *et al.* Author Correction: Statin treatment after acute coronary syndrome: Adherence and reasons for non-adherence in a randomized controlled intervention trial. Scientific reports 2021; 11:6454. http://www.ncbi.nlm.nih.gov/pubmed/?term=33723289
7. Du RW, Bu WG. Simvastatin Prevents Neurodegeneration in the MPTP Mouse Model of Parkinson's Disease via Inhibition of A1 Reactive Astrocytes. Neuroimmunomodulation 2021:1-8. http://www.ncbi.nlm.nih.gov/pubmed/?term=33735898
8. Cerda A, Bortolin RH, Manriquez V *et al.* Effect of statins on lipid metabolism-related microRNA expression in HepG2 cells. Pharmacological reports : PR 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33721286

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