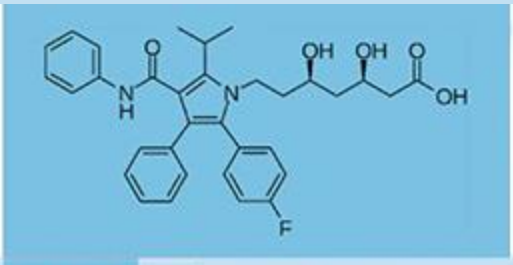
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 12, 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

Are hydrophilic statins less likely to produce muscle symptoms

Muscle-related adverse events are commonly reported in real-world clinical encounters and observational registries. This contrasts with reported muscle side effects in randomized clinical trials. In this retrospective analysis of the United Kingdom-based Clinical Practice Research Datalink (CPRD) GOLD, a UK registry with >15 million primary care patients. The objective was to compare the frequency of muscle-related events between equipotent lipophilic and hydrophilic statins. Using a propensity score-matched study design, 3 cohorts were created comparing 1) pravastatin 20-40 mg (hydrophilic) with simvastatin 10-20 mg; 2) rosuvastatin 5-40 mg (hydrophilic) with atorvastatin 10-80 mg and 3) simvastatin 40-80 mg with atorvastatin 10-20 mg. The study's primary outcome was the first reported muscular event (myopathy, myalgia, myositis, rhabdomyolysis) during a 1-year follow-up. The propensity-matched cohorts consisted of 9 703, 7 032, and 37 434 matched pairs of first-time statin users. The risk for developing muscular events resulted in an HR: 0.86 (0.64-1.16) for group 1, an HR: 1.17 (0.88-1.66 for group 2, and an HR: 1.33 (1.16-1.53) for group 3. Based on these findings, the authors concluded that equipotent hydrophilic statins were not

better tolerated compared to lipophilic statins.

Mueller AM, Liakoni E, Schneider C *et al.* The Risk of Muscular Events Among New Users of Hydrophilic and Lipophilic Statins: an Observational Cohort Study. Journal of general internal medicine 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33751411

Statin use associated with prolonged graft patency after lower extremity arterial by-pass

Long term graft patency after a lower extremity arterial by-pass (LEAB) was evaluated in this Korean single institute registry that collected data on 957 LEAB's. Patients were divided into 2 groups: graft patency <2-years and graft patency >5 years. In total 259 limbs were included: in group I, 125 limbs and in group II 134 limbs. Based on univariate analysis, long term patency was associated with younger age (69 years vs. 66 years, P = 0.024), hypertension (60.8% vs. 74.6%, P = 0.017), claudication (51.2% vs. 70.9%, P = 0.001), absence of prior intervention (50.4% vs. 73.9%, P < 0.001), common femoral artery-based bypass (57.6% vs. 70.1%, P = 0.035), above-the knee bypass (36.8% vs. 64.2%, P < 0.001), postoperative graft salvage procedure (3.2% vs. 14.8%, P = 0.001), and statin use (75.2% vs. 88.8, P = 0.004) were A multivariate analysis showed the following risk factors to be associated with reduced graft patency; hypertension OR: 1.91 (P = 0.038), claudication OR: 2.08 (P = 0.032), no prior intervention OR: 2.48 (P = 0.001), vein graft OR: 4.36 (P = 0.001), above-the knee bypass OR: 4.68 (P < 0.001), and graft salvage procedures OR: 7.70; P < 0.001) were identified as independent factors.

Jung KS, Heo SH, Woo SY *et al.* Factors associated with long-term graft patency after lower extremity arterial bypasses. Ann Surg Treat Res 2021; 100:175-185. http://www.ncbi.nlm.nih.gov/pubmed/?term=33748031

Effect of statin intensity on residual risk in ODYSSEY OUTCOMES trial

In this sub-analysis of the ODYSSEY OUTCOMES trial, the impact of statin intensity on outcomes. Of the 18 924 ACS patients included in the study, most used high-intensity statins 88.8%, 8.7% used moderate/low-intensity statins, and 2.4% did not use statins. The median baseline LDL-c in these three groups was 86,89 and 139 mg/dL. (P<0.001). The addition of alirocumab produced similar relative LDL-c reductions in all patients. However, the absolute LDL- reductions were significantly different; 52.9 mg/dl, 56.7 mg/dl, and 86.1 mg/dl, respectively (P<0.001). In the control arm, the incidence of MACE was highest in patients that did not use a statin (10.8%, 10.7%, and 26.0%, respectively). Patients that used alirocumab were able to reduce their risk of MACE in all three groups; HR: 0.88 (0.80–0.96); HR:0.68 (0.49–0.94); and HR: 0.65 (0.44–0.97), respectively. A gradient in the absolute risk

reduction was observed, 1.25% (0.34–2.16); 3.16% (0.38–5.94) and 7.97% (0.42–15.51); $P_{interaction}$=0.106. Using high-intensity statins is vital to prevent recurrences after an ACS; the addition of alirocumab can substantially reduce residual risk, but patients that did not use statins remained to have a high absolute risk for a recurrent MACE event. Diaz R, Li QH, Bhatt DL *et al.* Intensity of statin treatment after acute coronary syndrome, residual risk, and its modification by alirocumab: insights from the ODYSSEY OUTCOMES trial. Eur J Prev Cardiol 2021; 28:33-43. http://www.ncbi.nlm.nih.gov/pubmed/?term=33755145

Statins and skin cancer – unexpected finding in Icelandic whole population registries

A few reports have suggested that statin use is associated with an increased risk of developing keratocyte carcinoma (KC). By combining the Icelandic Cancer Registry and Icelandic Prescription Medicine Register, a whole population case-control study was designed to probe the relationship between statin used and the incidence of basal cell carcinoma (BCC; N= 4700), in situ squamous cell carcinoma (SCC is; N=11167) and invasive SCC (N=1013). Between 2003 and 2017. Each case was paired with ten age- and sex-matched controls. Overall statin use was associated with an increased risk of invasive SCC and SCCis but not BCC; aOR: 1.29 (1.11–1.50); 1.43 (1.24–1.64); 1.03 (0.95–1.120, respectively. Age was a significant modifier of this increased risk, patients>60 years of age were at increased risk, but this was not observed in younger (<60 years) patients. A disparity in risk was noted for different statins; atorvastatin use was associated with an increased risk for SCC is compared to simvastatin users that had a higher risk for developing SCCis and SCC. This study in the entire Icelandic population showed an association between statin use and the risk of developing certain skin cancer types in a low UV environment. This study's observational design can only point out associations; additional research is warranted to determine causality and explore the potential causes of these findings.

Adalsteinsson JA, Muzumdar S, Waldman R *et al.* Statins are associated with increased risk of squamous cell carcinoma of the skin: a whole-population study from Iceland. Arch Dermatol Res 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33772628

CVD risk reduction with equipotent atorvastatin 40 mg vs simvastatin 20 mg + ezetimibe 10 mg

Are there differences in CV outcome when comparing a high-intensity statin (atorvastatin 40 mg) with a moderate-intensity statin (simvastatin 20 mg) + ezetimibe 10 mg? Using the Taiwan National Health Insurance Research Database. Clinical outcomes were evaluated in 3 372 post-ACS diabetic patients diagnosed between January 1, 2007, and December 2013,

2013. The primary composite outcome includes CV death, non-fatal myocardial infarction, and non-fatal stroke. The secondary composite outcome includes hospitalization for unstable angina (HUA), percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). After a mean follow-up time of 2.4 years, the primary outcomes were not significantly different in the two cohorts, HR:1.09 (0.95–1.25). For the secondary outcomes, atorvastatin 40 mg showed a more pronounced benefit; HUA HR: 0.50 (0.35–0.72), PCI; HR: 0.82; (0.69–0.97) and CABG; HR: 0.62 (0.40–0.97). the authors noted that LDL-c reductions are comparable; the reduction of LDL-c by Atorvastatin 40 mg is less than that by ezetimibe 10 and simvastatin 20 mg, 48.3–49% vs. 50.6–51.9% respectively. The authors concluded that this study's results support the key role of LDL-C in the pathogenesis of ASCVD, and LDL-c lowering potency is the primary concern to reduce this risk. Kao YC, Chen TH, Liu CH *et al.* Similar major cardiovascular outcomes between pure statin and ezetimibe-statin in comparable intensity for type 2 diabetes with extremely atherosclerotic risks. Scientific reports 2021; 11:6697. http://www.ncbi.nlm.nih.gov/pubmed/?term=33758291

Relevant publications

1. Yetmar ZA, Challener DW, Tleyjeh IM *et al.* Association between Chronic Statin Use and 30-Day Mortality in Hospitalized Patients with COVID-19. Mayo Clinic proceedings. Innovations, quality & outcomes 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33748678
2. Stock JK. Reply to: "It's time to stop the nonsense of withholding lipid lowering therapy on account of age" and "The evidence around safe and effective LDL cholesterol-lowering therapy in elderly individuals demands validity and clinical relevance". Atherosclerosis 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33762114
3. Silvano J, Marques N, Tavares I, Ferreira I. Severe L-asparaginase-induced Hypertriglyceridaemia Treated with Plasmapheresis. European journal of case reports in internal medicine 2021; 8:002342. http://www.ncbi.nlm.nih.gov/pubmed/?term=33768080
4. Sarfo FS, Adamu S, Obese V *et al.* Atherosclerotic event risk and risk reduction therapies among Ghanaian hemorrhagic stroke survivors. J Neurol Sci 2021; 424:117389. http://www.ncbi.nlm.nih.gov/pubmed/?term=33773409
5. Sammour Y, DeZorzi C, Austin BA *et al.* PCSK9 Inhibitors in Heart Transplant Patients: Safety, Efficacy, and Angiographic Correlates. J Card Fail 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33753241
6. Rinehart SN, Collins C, Glover J, Rice WM. Evaluation of a pharmacist-driven medication adherence enhancement service. Journal of managed care & specialty pharmacy 2021; 27:507-515. http://www.ncbi.nlm.nih.gov/pubmed/?term=33769859

7. Petrov I, Postadzhiyan A, Vasilev D *et al.* Familial Hypercholesterolemia Identification Algorithm in Patients with Acute Cardiovascular Events in A Large Hospital Electronic Database in Bulgaria: A Call for Implementation. Adv Ther 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33754300
8. Mylonas KS, Iliopoulos D, Nikiteas N, Schizas D. Looking for the Achilles heel of atheromatosis: could it be immunotherapy? Immunotherapy 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33757293
9. Masson W, Rossi E, Alvarado RN *et al.* Rheumatoid Arthritis, Statin Indication and Lipid Goals: Analysis According to Different Recommendations. Reumatologia clinica 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33745866
10. Lei HP, Qin M, Cai LY *et al.* UGT1A1 rs4148323 A Allele is Associated With Increased 2-Hydroxy Atorvastatin Formation and Higher Death Risk in Chinese Patients With Coronary Artery Disease. Frontiers in pharmacology 2021; 12:586973. http://www.ncbi.nlm.nih.gov/pubmed/?term=33762934
11. Koskinas KC, Gencer B, Nanchen D *et al.* Eligibility for PCSK9 inhibitors based on the 2019 ESC/EAS and 2018 ACC/AHA guidelines. Eur J Prev Cardiol 2021; 28:59-65. http://www.ncbi.nlm.nih.gov/pubmed/?term=33755142
12. Kim BS, Chan N, Hsu G *et al.* Sex Differences in Coronary Arterial Calcification in Symptomatic Patients. Am J Cardiol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33757786
13. Hermann R, Gundlach K, Seiler D. Mechanistic Considerations About an Unexpected Ramipril Drug-Drug Interaction in the Development of a Triple Fixed-Dose Combination Product Containing Ramipril, Amlodipine, and Atorvastatin. Clinical pharmacology in drug development 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33773093
14. Kaplan DE, Mehta R, Garcia-Tsao G *et al.* SACRED: Effect of simvastatin on hepatic decompensation and death in subjects with high-risk compensated cirrhosis: Statins and Cirrhosis: Reducing Events of Decompensation. Contemporary clinical trials 2021; 104:106367. http://www.ncbi.nlm.nih.gov/pubmed/?term=33771685
15. Hennig M, Brandt A, Bautembach-Minkowska J *et al.* When do paediatric patients with familial hypercholesterolemia need statin therapy?(). J Mother Child 2021; 21:43-50. http://www.ncbi.nlm.nih.gov/pubmed/?term=33751874
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17. Cohen H, Durst R, Elis A *et al.* [TREATMENT OF HOMOZYGOTES OF FAMILIAL HYPERCHOLESTEROLEMIA: RECOMMENDATIONS OF THE ISRAELI SOCIETY OF ATHEROSCLEROSIS]. Harefuah 2021; 160:170-174. http://www.ncbi.nlm.nih.gov/pubmed/?term=33749180
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19. Wiklund O. [Elderly benefit from lower LDL-cholesterol]. Lakartidningen 2021; 118. http://www.ncbi.nlm.nih.gov/pubmed/?term=33768516
20. Welty FK, Schulte F, Alfaddagh A *et al.* Regression of human coronary artery plaque is associated with a high ratio of (18-hydroxy-eicosapentaenoic acid + resolvin E1)

to leukotriene B(4). FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2021; 35:e21448. http://www.ncbi.nlm.nih.gov/pubmed/?term=33749913
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22. Valladales-Restrepo LF, Medina-Morales DA, Giraldo-Giraldo C, Machado-Alba JE. Prescription of statins and pharmacokinetic interactions in Colombian patients. Expert Opin Drug Metab Toxicol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33759676
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24. Lima Cunha D, Richardson R, Tracey-White D *et al.* REP1-deficiency causes systemic dysfunction of lipid metabolism and oxidative stress in choroideremia. JCI insight 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33755601
25. Boettiger DC, Newall AT, Phillips A *et al.* Cost-effectiveness of statins for primary prevention of atherosclerotic cardiovascular disease among people living with HIV in the United States. Journal of the International AIDS Society 2021; 24:e25690. http://www.ncbi.nlm.nih.gov/pubmed/?term=33749164
26. Baliga MM, Klawitter J, Christians U *et al.* Metabolic profiling in children and young adults with autosomal dominant polycystic kidney disease. Scientific reports 2021; 11:6629. http://www.ncbi.nlm.nih.gov/pubmed/?term=33758231
27. Albassam AA, Alanazi A, Alhaqbani N *et al.* The potential of drug-herbal interaction among patients with chronic diseases in Saudi Arabia. Complement Ther Clin Pract 2021; 43:101324. http://www.ncbi.nlm.nih.gov/pubmed/?term=33765548

Basic Science publications

1. Yazdani Ashtiani S, Ahmad Nasrollahi S, Naeimifar A *et al.* Preparation and Safety Evaluation of Topical Simvastatin Loaded NLCs for Vitiligo. Advanced pharmaceutical bulletin 2021; 11:104-110. http://www.ncbi.nlm.nih.gov/pubmed/?term=33747857
2. Wang H, Wang T, Zhang Z *et al.* Simvastatin inhibits oral squamous cell carcinoma by targeting TMEM16A Ca(2+)-activated chloride channel. Journal of cancer research and clinical oncology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33755783

3. **Mounier NM, Wahdan SA, Gad AM, Azab SS. Role of inflammatory, oxidative, and ER stress signaling in the neuroprotective effect of atorvastatin against doxorubicin-induced cognitive impairment in rats. Naunyn-Schmiedeberg's archives of pharmacology 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33755739
4. **Menze ET, Ezzat H, Shawky S *et al.* Simvastatin mitigates depressive-like behavior in ovariectomized rats: Possible role of NLRP3 inflammasome and estrogen receptors' modulation. Int Immunopharmacol 2021; 95:107582.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33774267
5. **Li HX, Liang XY, Wu JH *et al.* Simvastatin attenuates acute lung injury by activation of A2B adenosine receptor. Toxicology and applied pharmacology 2021:115460.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33774062
6. **Iqbal R, Qureshi OS, Yousaf AM *et al.* Enhanced solubility and biopharmaceutical performance of atorvastatin and metformin via electrospun polyvinylpyrrolidone-hyaluronic acid composite nanoparticles. Eur J Pharm Sci 2021; 161:105817.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33757829
7. **Chen N, Ren R, Wei X *et al.* Thermoresponsive Hydrogel-Based Local Delivery of Simvastatin for the Treatment of Periodontitis. Molecular pharmaceutics 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=3375472

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